Sport-related sudden cardiac death

Causes and prevention

Pietro Delise
Paolo Zeppilli
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Preface

Sudden cardiac death is rare in athletes. However, it has devastating psychological effects. Indeed, ordinary people do not understand how subjects capable of exceptional physical performances, who theoretically should be more resistant than the normal population, can die suddenly.

The explanation is that athletes who die suddenly have an unknown heart disease which does not reduce their physical performance. Indeed, many such diseases frequently do not cause symptoms and are difficult to diagnose. This is the case of primary genetic cardiomyopathies (such as right and left arrhythmogenic cardiomyopathy and hypertrophic cardiomyopathy). Some of these diseases are aggravated by effort and, when unrecognized, may lead to sudden death owing to malignant ventricular arrhythmias. The challenge is to diagnose them as earlier as possible.

In Italy, the problem of health and medical assistance for athletes has been particularly felt for many years. In 1929, the Italian Olympic Committee created a Federation exclusively dedicated to sports medicine, the Italian Federation of Sports Medicine (FMSI). Furthermore, in 1957, Professor Margaria founded the postgraduate school of Sports Medicine in Milan, which was the first in the world. Finally, in 1981, the Italian Society of Sports Cardiology (SIC Sport) was founded.

This cultural background favored the diffusion of sports medicine in Italy, culminating in 1982 in a specific law aimed at protecting the health of those involved in competitive sports. According to this law, responsibility for the certification of an athlete's health and eligibility for competitive sports was assigned to a specialist in sports medicine. The law also gave rise to the world's first pre-participation model of cardiovascular screening by means of the electrocardiogram (ECG), a simple instrumental method which can help to unmask many suspected heart diseases.

The Italian model was progressively exported to many other nations, especially in Europe, and scientifically endorsed by prestigious researchers and institutions, such as the IOC (International Olympic Committee).

Since 1989, the Italian Society of Sports Cardiology (SIC Sport) and the Italian Federation of Sports Medicine (FMSI), in collaboration with the main Italian Cardiological Scientific Societies (ANCE, ANMCO, and SIC), have produced the Italian Cardiological Guidelines for Competitive Sports Eligibility in athletes with heart disease. The English version of these guidelines was published in 2013 in the Journal of Cardiovascular Medicine [1, 2]. An update of these guidelines was subsequently published in 2020 in the same journal.

The effectiveness of the Italian screening model has been repeatedly confirmed at the scientific level in recent decades. Indeed, about 20 years after the law came into force, the incidence of sudden cardiac death among Italian athletes was seen to have decreased by about 90% [3].

This important cultural background has prompted several Italian researchers to publish a number of studies in the most important international cardiologic journals.

When Springer Nature asked me to edit this book, I accepted enthusiastically and decided to involve only Italian authors, who are among those who have published famous articles which have been read throughout the world.

I apologize to all the famous non-Italian authors, but this book is mainly a celebration of the Italian School in the field of the prevention of sudden death in athletes.

Verona, Italy — Pietro Delise
Roma, Italy — Paolo Zeppilli

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Contents

Sudden Death in Athletes: Autoptic Findings

1

Gaetano Thiene, Cristina Basso, Donata Favretto, and Stefania Rizzo

1.1 Introduction

There is no doubt that exercise and sport activity are beneficial to health [1]. However, effort may trigger malignant arrhythmias at risk of sudden death (SD) in people affected by concealed cardiac diseases. SD in athletes is threefold more frequent than in sedentary young [2, 3].

The "Achilles heel" (Fig. 1.1) is located in one of the basic components of the heart: great vessels, coronary arteries, myocardium, valves, conduction system, and ion channels. A thorough postmortem examination of fatal cases is mandatory, including toxicology [4, 5] and molecular investigation ("molecular autopsy"), in search of viral infections or genetic mutations [6, 7].

In this chapter, we will deal with the diseases that cause SD in the young athletes (<40 years old), based upon our long-standing experience on the study of hundreds of cases in the young and in athletes, collected since 1980, in a prospective autopsy investigation of all cases occurred in the Veneto Region (Italy), with prevention implications [8–11].

According to our early data, SD in the young can be cardiac in 91% of fatal cases, cerebral (hemorrhage due ruptured of berry aneurysm of Willis circle) in 5% [10–12], and respiratory (allergic bronchial asthma) in 4% [10, 13, 14]. As far as the mechanism of cardiac SD, it can be arrhythmic (usually ventricular fibrillation) in

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Fig. 1.1 The Greek myth of Achilles heel, pierced by Paris's arrow

93% or mechanical (pulmonary thromboembolism or aortic rupture with cardiac tamponade) in 7% [8, 10]. Ventricular fibrillation remains the major nightmare.

Cardiovascular causes of sudden cardiac death should be searched at the following levels:

1.2 Aorta and Pulmonary Artery

Abrupt dissection of the aorta in the young usually occurs in the setting of predisposing factors, whether genetically determined like Marfan syndrome (Fig. 1.2) [15] or congenital heart disease (CHD) like bicuspid aortic valve (BAV) (Fig. 1.3), with or without isthmic coarctation [16–18]. They both show severe degeneration of tunica media (medionecrosis, loss of elastic lamellae or fragmentation, mucoid substance accumulation), prone to spontaneous wall laceration (Figs. 1.2b and 1.3b).

As far as BAV, the predictive risk factor to dissection is the coexistence of an aortopathy, quite similar to that of Marfan syndrome, accounting for aortic wall fragility and spontaneous, nontraumatic rupture [19].

BAV is the more frequent CHD with a prevalence of 1–1.5% in the general population [20–22]. It is a classical CHD which may remain concealed until adulthood, since the valve may regularly function, without stenosis or incompetence, and silent without murmur at auscultation. The diagnosis in vivo is feasible with a two-dimensional (nowadays, even tridimensional) echo, able to demonstrate the existence of two cusps, one with a raph which is an aborted commissure [23] since development in the embryo [24].

The measure of the ascending aorta diameter is fundamental to establish the existence of aortopathy. The border-line size for surgical replacement of the aorta to

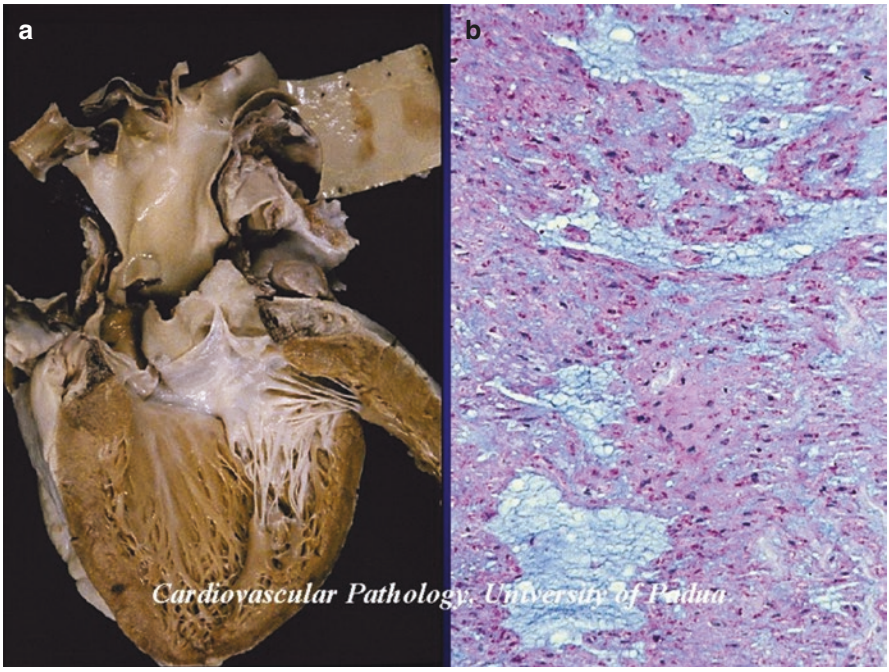

Fig. 1.2 Aortic dissection in a 22-year-old male, basketball player with Marfan syndrome, and external rupture (**a**), cardiac tamponade, and sudden death. Note cystic medial necrosis in the aortic wall at histology (**b**). Alcian Pas stain (Taken from *Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3*)

prevent dissection has been established in 5 cm [25]. However, we have seen cases of SD with BAV, spontaneous aortic rupture with smaller diameter (<4 cm) and massive loss of elastic lamellas at the histology of the aortic wall (Fig. 1.3). Assessment in vivo of elasticity and stiffness by echo (systo-diastolic excursion of the aorta) seems to be more reliable to predict fragility of the tunica media [26].

Pulmonary thromboembolism rarely occurs in young females taking contraceptives [27]. We had a case, happened during swimming, of a 24-year-old girl under contraceptives therapy.

1.3 Coronary Arteries

They may be involved by acquired disease or congenital malformations [28–30].

Coronary atherosclerosis may prematurely develop in the young and athletes with such severity to obstruct the lumen, thus creating myocardial ischemia and triggering ventricular fibrillation with cardiac arrest. Of course, effort facilitates an imbalance of coronary blood supply.

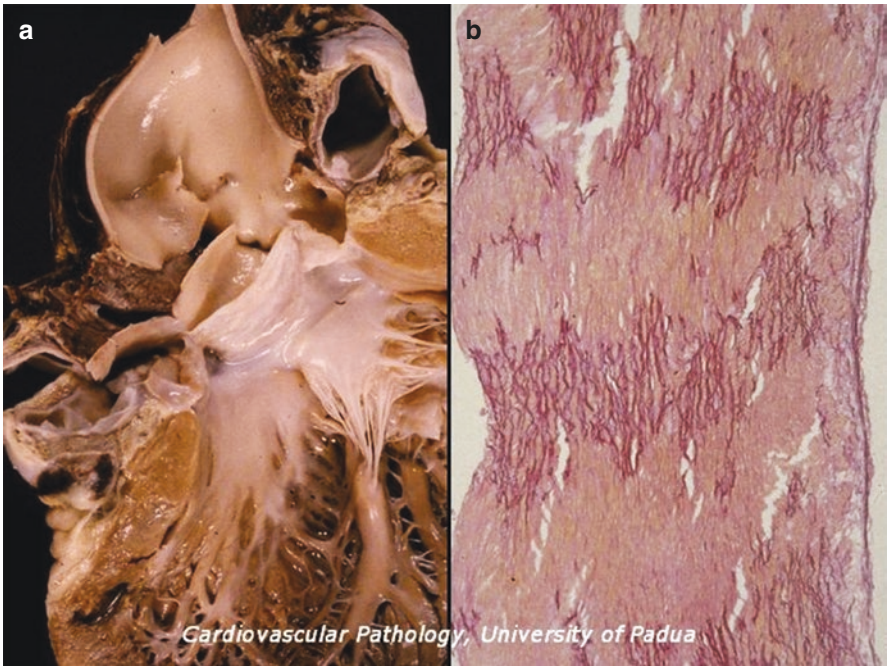

Fig. 1.3 A 24-year-old male with SD at rest due to aortic dissection in bicuspid aortic valve with cardiac tamponade. The diameter of the tubular ascending aorta was 37 mm. Note the intimal tear in the ascending aorta (**a**) and the severe elastic loss in the tunica media of ascending aorta (**b**). Weigert Van Gieson stain (Taken from Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3)

In almost all the cases, a single atherosclerotic plaque was found at the level of a proximal-middle segment of the descending coronary artery ("the SD coronary artery") [31] (Fig. 1.4).

The occlusion may be the consequence of thrombosis (Fig. 1.5) or vasospasm in correspondence of an atherosclerotic plaque consisting of smooth muscle cell proliferation and no atheroma (Fig. 1.4) [32]. The intimal muscle cells are synthetic or even contractile, the latter most probably contributing to vasospasm [33–35].

At difference from adults, where thrombosis occurs over a ruptured fibrous cap [36, 37], thrombosis in the young is observed upon endothelial erosion due to inflammation of the endothelium ("endotheliitis") (Fig. 1.5) [38, 39]. Vasospasm may cause transient occlusion and myocardial ischemia (Fig. 1.4). Reperfusion, at the reopening of the vessel, may trigger ventricular fibrillation [32, 40–42].

Only one-third of SD cases show occlusive thrombus, whereas two-thirds exhibit a critical plaque with likely superimposed vasospasm [31, 32].

An acute myocardial infarction has never been observed, because the onset of ventricular fibrillation with cardiac arrest occurs immediately following organic or functional coronary occlusion, well before that gross and histologic injury can become evident [31].

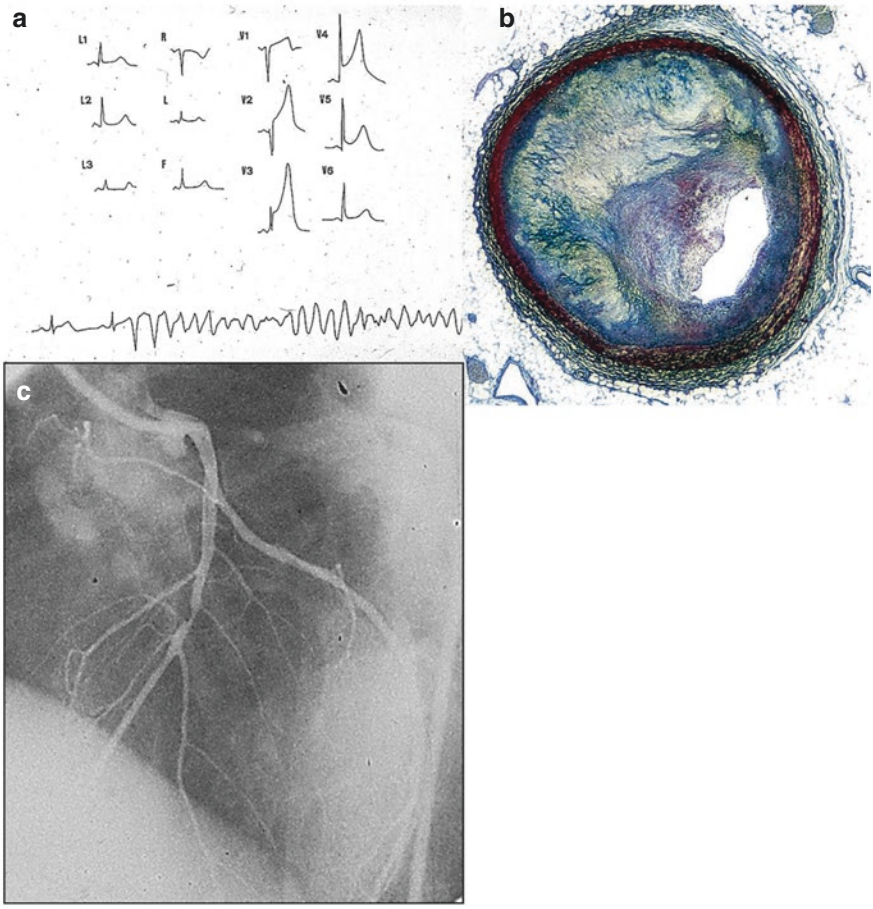

Fig. 1.4 (**a**) Transient ST segmental elevation in a 40-year-old man triggering ventricular fibrillation. (**b**) Previous selective coronary arteriography: single atherosclerotic plaque is found located in the anterior descending coronary artery. (**c**) At histology eccentric plaque without necrotic core and intimal proliferation of smooth muscle cells, with preserved tunica media. (Adapted from Corrado et al. Int J Cardiol 1990; 26:361–7 [32]). Azan Mallory Heidenhain stain. (Taken from Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3)

Erosion thrombosis may occur over a noncritical plaque, which escapes at stress ECG test, thus rendering the thrombotic complication unpredictable [9].

As far as the prevalence of atherosclerotic SD, it increases with age, being almost absent under 20 years, appearing occasionally in the time interval 20–30 years and reaching a major role in the age interval 31–40, as to become the most frequent cause of SD in the young in this time interval [9, 10, 31].

Other acquired causes of coronary occlusion (arteritis, dissection, embolism) are exceeding rare [43–45].

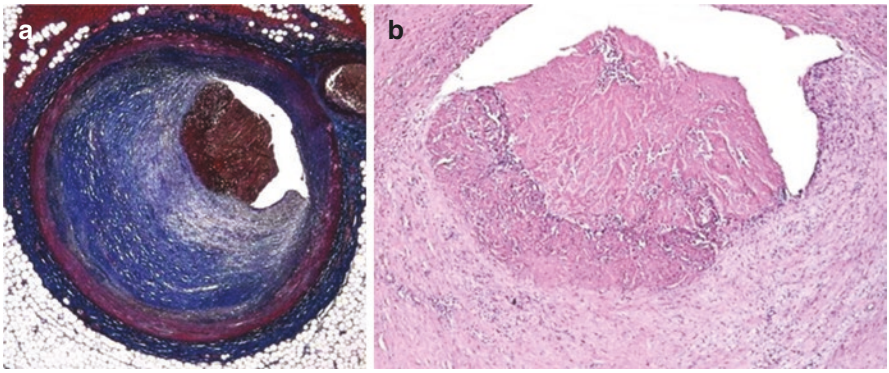

Fig. 1.5 Sudden death of a 31-year-old male. Histologic transverse section of the proximal left anterior descending coronary artery. (**a**) An eccentric fibrocellular plaque devoid of lipid core, complicated with occlusive thrombosis by erosion (Azan Heidenhain, ×5). (**b**) Close-up of panel (**a**): two separate layers of thrombus deposition, mostly platelets fresh and subacute with fibrosis and early organization, are detected (hematoxylin–eosin, ×12). Toxicological analysis revealed high levels of cocaine and cannabis. (Adapted from Montisci M et al., Cardiovasc Pathol. 2008;17:344–6 [4])

Coronary artery anomalies are the third cause of sudden death in athletes, in terms of prevalence, after arrhythmogenic cardiomyopathy (AC) and coronary atherosclerosis [3, 20]. Origin from wrong aortic sinus, whether left coronary artery from the right sinus (Fig. 1.6a) or right coronary artery from the left sinus, is a hidden malformation since it does not manifest myocardial ischemia neither at basal nor at stress ECG tests [46–49].

The first tract of the anomalous coronary artery runs between the aorta and the pulmonary artery (Fig. 1.6b) or even intramural within the aortic wall, with a slit-like lumen (Fig. 1.6c). During prolonged effort like running, a discrepancy develops between demand and supply of coronary blood flow. This precipitates myocardial ischemia with patchy cardiomyocyte necrosis and then scarring, a quite malignant combination.

Myocardial bridge of the first tract of the descending coronary artery is a controversial cause of sudden death in the young, being a frequent observation even in normal hearts (30% of cases). Deep long intramural course with a coat of disarrayed myocardium surroundings the coronary segment is considered essential for causing transient ischemia and ventricular fibrillation [50].

Myocardial bridging has first been reported as a cause of sudden death by Morales et al. [51]. Oddly enough, by reviewing the illustrations of this paper, the hearts appear affected by hypertrophic cardiomyopathy (HCM), a cardiomyopathy in which myocardial bridging is so frequent (50% of cases) as to be regarded as a phenotypic expression of the disease [52]. However, whether SD in HCM is related to myocardial bridging has been questioned, since it may occur with or without bridging [52, 53].

Another intriguing coronary artery anomaly is the origin of the left circumflex coronary artery from the right aortic sinus or from the right coronary artery itself,

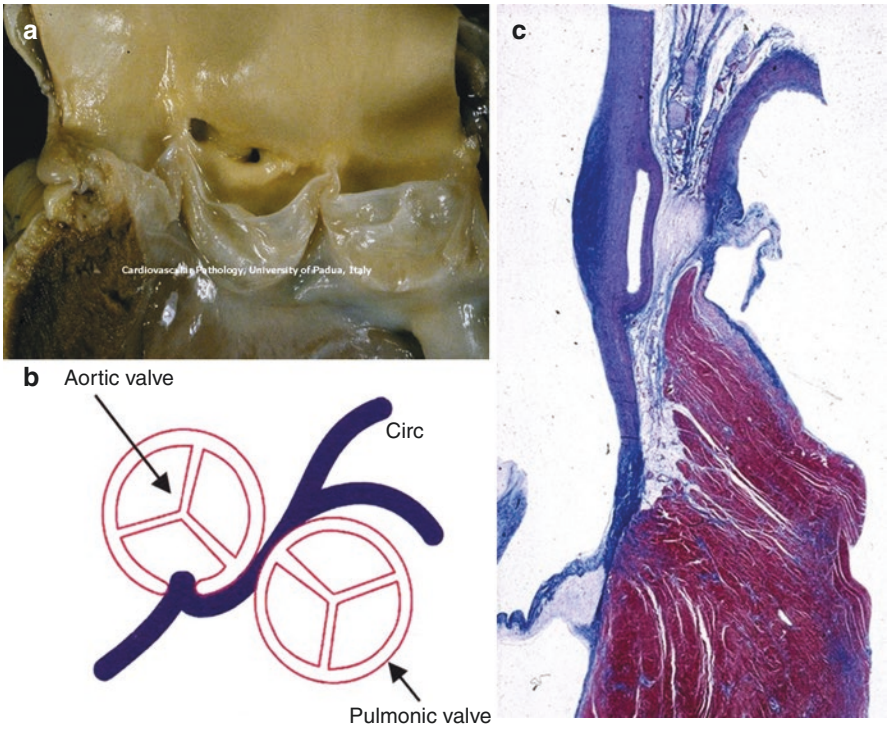

Fig. 1.6 A 28-year-old female who died during running. (**a**) View of the aorta root with two coronary orifices in the right aortic sinus. (**b**) Note the anomalous course between the aorta and the pulmonary artery of the left coronary artery originating from the right aortic sinus. (**c**) The course of the proximal anomalous left coronary artery is intramural within the aortic tunica media. Azan Mallory Heidenhain stain

with a retro-aortic course. Apparently a normal variant, it has been reported as an infarct-related artery in the absence of atherosclerotic plaques [54].

1.4 Myocardium

Primary myocardial diseases play a pivotal role as a cause of SD in athletes. As far genetically determined cardiomyopathies, *arrhythmogenic cardiomyopathy* (AC), a genetic disease of desmosome [55–59] is the leading cause of SD in athletes in our country. It consists of transmural involvement of the right ventricular free wall by fibrofatty replacement with thinning, accounting for aneurysms in the "triangle of dysplasia (inflow, apex, outflow) [56]. The ventricular septum and the left ventricle are spared, thus explaining the paradox of a preserved mechanical performance of the heart, able to face even extraordinary contractile demand during effort (Fig. 1.7). The rate of SD by AC is much higher in athletes vs the young with sedentary activity (odd ratio = 5.4) [2]. Reentry of the electrical impulse transmission within the

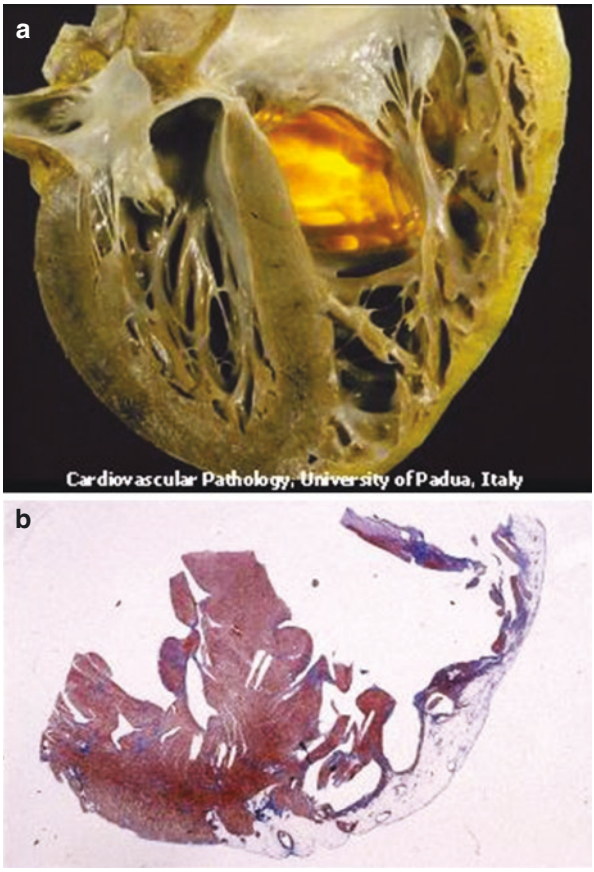

Fig. 1.7 Arrhythmogenic cardiomyopathy. (**a**) Gross four-chamber view with fibrous fatty replacement of RV with the translucent free wall. Note that the left ventricle and ventricular septum appear spared. (**b**) The same at histology. Azan Mallory Heidenhain stain

injured myocardium can trigger tachyarrhythmias with left bundle branch block morphology and even ventricular fibrillation during effort.

Recently, a left ventricular variant of AC has been reported in athletes, featured by fibrofatty scars in the subepicardium of the left ventricle [60–62]. The posterolateral location renders difficult detection by the ECG at precordial leads, thus escaping the visit for eligibility (Fig. 1.8).

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the sarcomere [64], characterized by asymmetric septal hypertrophy in the left ventricle and infarct like scars within (Fig. 1.9), is a leading cause of SD of athletes in the USA (reported up to 30% of cases) [53, 65–67], where visit for eligibility is accomplished without ECG and 2D echo, which is the in vivo diagnostic gold standard. The frequency of SD is much less in Italy [3], where eligibility is given on the basis of ECG and 2D echo. We have proven that it makes the difference [66–68]. Fibrotic scar within the asymmetric hypertrophy may be the source of fatal arrhythmias [67].

Myocarditis, an inflammatory disease of cardiac muscle, has been only occasionally observed in athletes as a cause of SD, because the associated symptoms like fever and dyspnea discourage sport activity participation. The rare cases observed

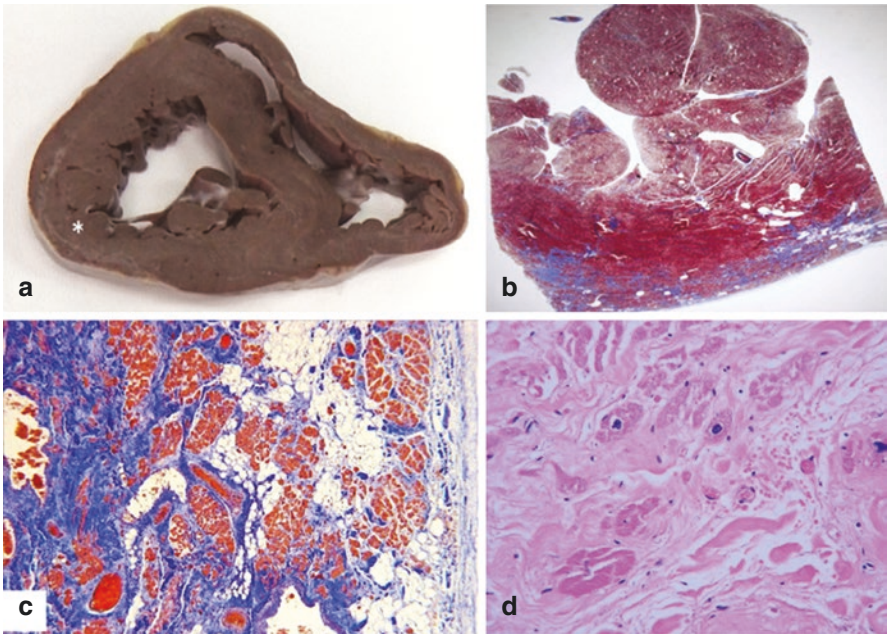

Fig. 1.8 Sudden death of a 25-year-old male football athlete due to left ventricular AC. (**a**) Cross section of the ventricles shows the normal right ventricular free wall and ventricular septum, whereas a scar is visible in the posteroinferior wall of the left ventricle. (**b**) At histology, the scar consists of fibrofatty replacement in the subepicardium. (**c**) Close-up of **b**. (**d**) At HE staining, note replacement-type fibrosis and dysmorphism of the cardiomyocytes. (Adapted from D'Amati et al., Int J Cardiol. 2016;206:84–6 [63]). (**b**, **c**) Azan Mallory Heidenhain stain. (**d**) Hematoxylin-eosin

did not disclose massive lymphocytic or giant cell inflammatory infiltrates of the fulminant myocarditis with cardiogenic shock (Fig. 1.10). On the opposite, they exhibit inflammatory infiltrates with interstitial edema and scanty myocyte necrosis, just enough to jeopardize the electrical stability of the heart. In vivo the disease, when suspected, may be diagnosed by magnetic resonance highlighting the inflammatory edema and by endomyocardial biopsy, which remains the diagnostic gold standard. Recovery may be accomplished by rest, drug therapy, and a temporary jacket with a defibrillator, just in case of a life-threatening arrhythmia [8–10, 69, 70].

1.5 Valve Disease

Mitral valve prolapse has been proven to be an arrhythmic disorder at risk of cardiac arrest, when the leaflets remodeling with mucoid thickening, hoodings, and chordal thinning/elongation are associated with fibrosis of the papillary muscles or the posterolateral myocardium (Fig. 1.11), which represents the arrhythmic substrate.

This morbid entity has been named arrhythmic mitral valve syndrome [71–73]. The disease is easily suspected by auscultation of systolic murmur and click at

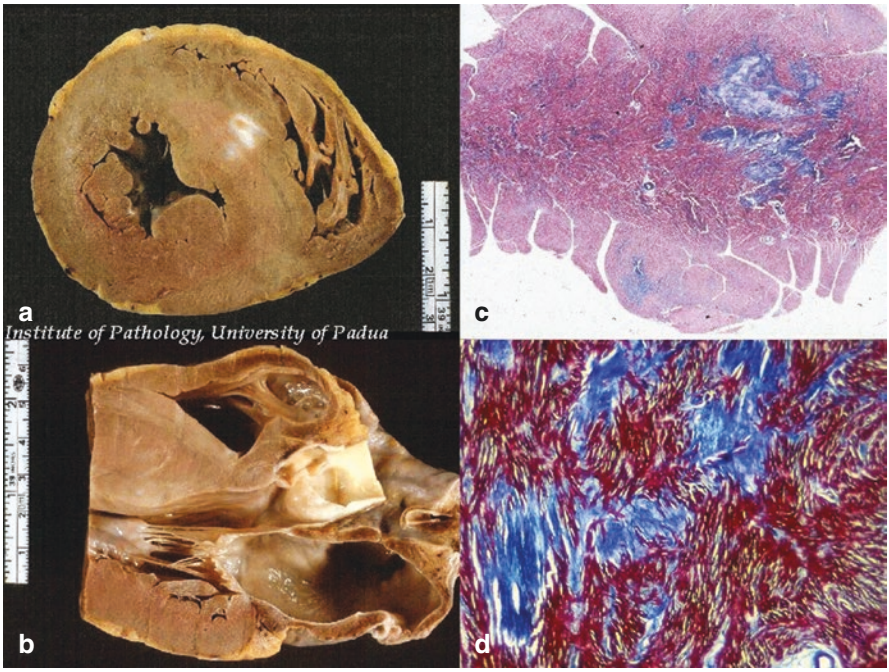

Fig. 1.9 Sudden death occurred during gymnastics in a 20-year-old recruit soldier. (**a**) Cross section of the ventricles. Note the asymmetric hypertrophy of the ventricular septum and a scar within. (**b**) Lung axis showing the asymmetric septal hypertrophy. (**c**) Panoramic histology view of the scar. (**d**) Close-up: disarray and fibrosis. Azan Mallory Heidenhain stain. (Taken from Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3)

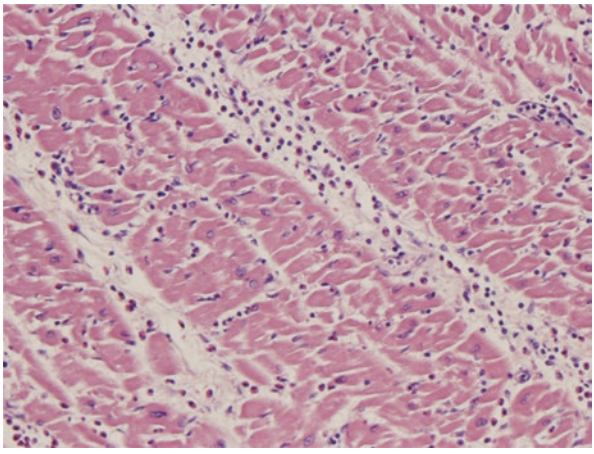

Fig. 1.10 Interstitial myocarditis with edema in the absence of myocyte necrosis, in a 19-year-old boy who died suddenly. Hematoxylin-eosin stain

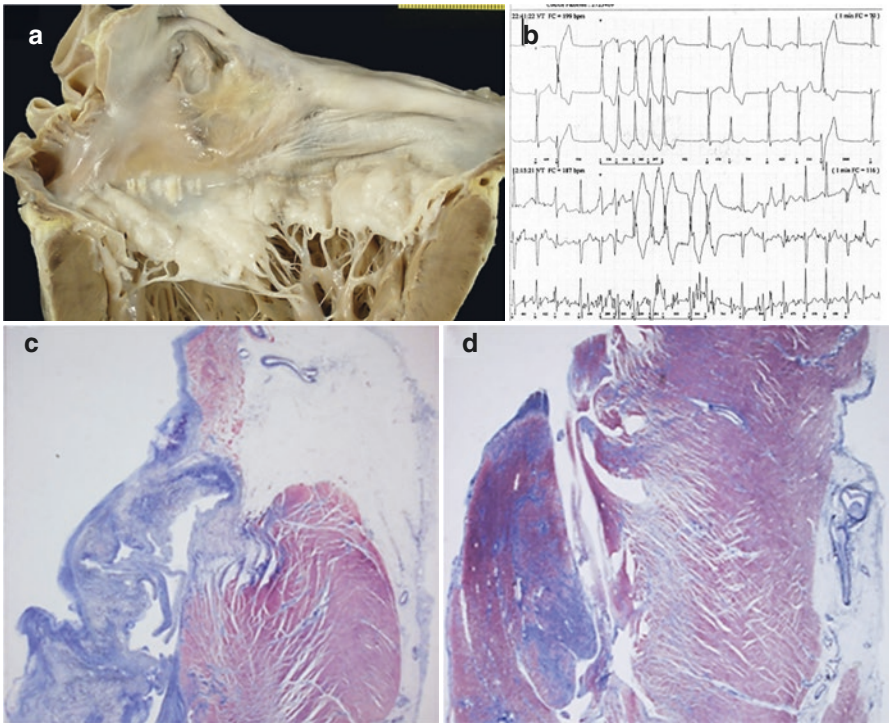

Fig. 1.11 Sudden death of a young female with arrhythmogenic mitral valve prolapse syndrome. (**a**) Gross view of the mitral valve with the classical remodeling of prolapse (thickness and hoodings of the leaflets). (**b**) Ventricular arrhythmias recorded at the ECG. (**c**) Mucoid leaflet degeneration and thickening. (**d**) Fibrosis of the posteromedial mitral papillary muscle. Azan Mallory Heidenhain stain

auscultation and by prolapsing mitral leaflets in the left atrium during systole by echo. Magnetic resonance with late enhancement is able to detect fibrosis in vivo [71].

Ventricular arrhythmias are recorded at Holter meeting. Murmur is easily heard, and 2D is part of the physical examination for sport eligibility in Italy. Thus, SD by MVP is a quite rare occurrence in our country [3].

1.6 Conduction System

As far as pathology of conduction system at risk of SD, *ventricular preexcitation* represents the main life-threatening condition. Wolff-Parkinson-White syndrome is a congenital, microscopic defect with an accessory fascicle of working myocardium connecting the atria with the ventricles, outside the regular specialized AV conduction system, accounting for episodes of reentry supraventricular tachycardia (Fig. 1.12b) [74–77].

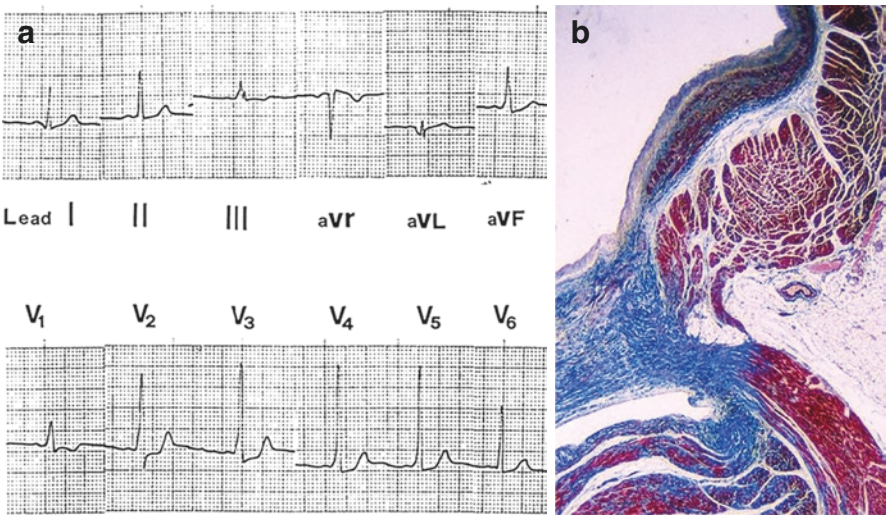

Fig. 1.12 Sudden death of a 24-year-old male student affected by ventricular preexcitation. (**a**) Baseline ECG with delta wave and short PQ. (**b**) A small myocardial bundle connects the left atrial with the left ventricular myocardium. It is quite close to the endocardium, behind the mitral AV ring, thus easy to be ablated. Azan Mallory Heidenhain stain. (Taken from Thiene G, Corrado D, Basso C. Sudden Cardiac Death in the Young and Athletes. Text Atlas of Pathology and Clinical Correlates. Springer-Verlag Mailand 2016. Springer-Verlag Milan. X, 190. ISBN 978-88-470-5775-3)

Since it is quite easy to detect at basal ECG (short QT and delta wave) (Fig. 1.12a) at the time of screening for eligibility, the affected people are regularly disqualified in Italy from sport activity; thus, ventricular preexcitation as a cause of sudden death in athletes is quite rare in our country.

The accessory pathway of the working myocardium is not gifted by refractory conduction. Thus, it allows a speedy transfer of the electrical impulse from the atria to the ventricles, with preexcitation. Reentry supraventricular tachycardia may be orthodromic or antidromic, according to the impulse direction along the specialized AV conduction system.

Bursts of paroxysmal atrial fibrillation, in the presence of an accessory AV bundle with a short refractory period, may conduct one-to-one from the atria to the ventricles, with the risk of transform atrial fibrillation into ventricular fibrillation with cardiac arrest and sudden death. Isolated atrial myocarditis has been advanced as a possible culprit of paroxysmal atrial fibrillation [77].

1.7 Ion Channel Diseases: Sudden Death with Structurally Normal Heart

Some hearts from SD in the young and athletes may appear normal, even after a thorough investigation ("mors sine materia"). Most of them show specific ECG signs (long and short QT, nonischemic ST segment elevation), due to sodium or potassium channel genetic mutations [78]. The ECG abnormalities are easily identified at sport eligibility and then the athletes are disqualified.

A recently discovered syndrome (catecholaminergic polymorphic ventricular tachycardia) [79] shows normal basal ECG and electrical ventricular instability with tachyarrhythmia triggered by effort or emotion, when the number of heartbeats exceeds the threshold of 120–130 bpm. Clearly, this disease may escape screening for eligibility, unless stress test ECG is performed.

It is a hereditary dominant disease due to mutations of the gene coding ryanodine receptor 2 in charge of intracellular Ca++ release from smooth sarcoplasmic reticulum for excitation-contraction coupling [80].

Unexplained SDs with structuraly normal heart, investigated by molecular genetic analysis ("molecular autopsy") (Fig. 1.13), have shown that ryanodine receptor II gene mutations are the most frequent cause, although the large majority of mors sine materia remains still unexplained (Fig. 1.14).

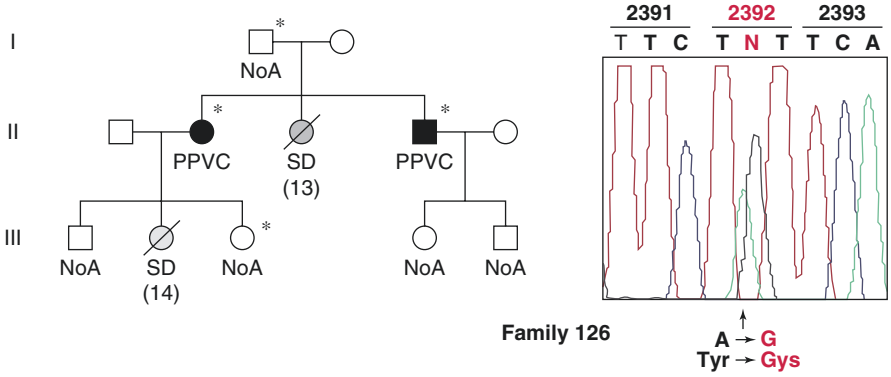

Fig. 1.13 The genealogic tree of a family with two young girls who died while swimming and running upstairs, respectively. Genetic investigation found just a pin-point mutation of the gene of the ryanodine receptor II protein, coding a defective amino acid. (Adapted from Bauce B et al., J Am Coll Cardiol. 2002;40:341–9 [81])

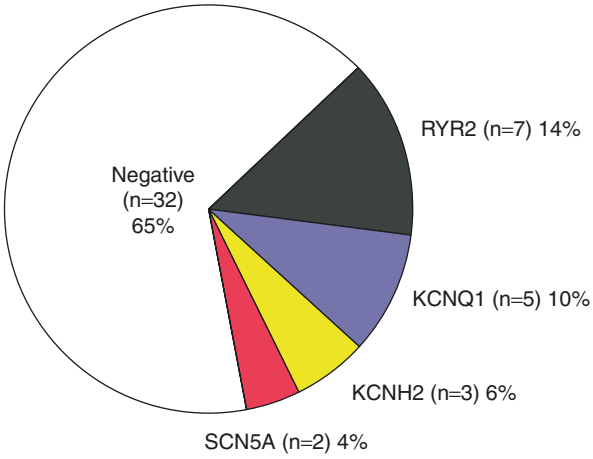

Fig. 1.14 Mutation of ryanodine receptor 2 is the leading cause of SD in the young with a normal heart. Note however that two-thirds of cases remain unexplained. (Adapted from Tester DJ et al., J Am Coll Cardiol. 2007;49:240–246 [82])

Table 1.1 Main causes of SD in the young and/or athletes (autopsy-proven)

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

Values are % unless otherwise indicated

Incidence of various causes of sudden death in the young on athletes. Note the extreme variability of the rate of sudden death with normal heart, among the reported experience. (Adapted from Thiene G et al, J Am Coll Cardiol. 2019;73:3031-3032 [83])

AC arrhythmogenic cardiomyopathy, *CAA* coronary artery anomaly, *CAD* atherosclerotic coronary artery disease, *HCM* hypertrophic cardiomyopathy, *MVP* mitral valve prolapse, *NA* not available

[a]Only competitive athletes

According to our large, long-standing experience of SD in the young (athletes included), the rate of SD with normal hearts is 17%, a difference from other studies where a rate of even 45–50% has been reported (Table 1.1) [83].

The expertise and skill to carry out autopsy is the most reasonable explanation [7]. Some groups acted as a referral center, thus collecting only intriguing cases as second opinion, especially cases apparently without an otherwise structural explanation.

There are several hypotheses to explain a skipped diagnosis: focal myocarditis for sampling error; hidden coronary artery disease for missed check of coronary orifices; longitudinal opening of the subepicardial coronary arteries, thus underestimating the severity of atherosclerotic plaques; undetected nonischemic ventricular scars by lack of multiple cross sections of the ventricles; missed concealed preexcitation syndrome, in the absence of ECG and serial histologic sections including AV rings; still unknown genetic disorders and mutations; lack of molecular autopsy and toxicological investigations.

We have to acknowledge the existence of investigative limits about the ability of the pathologist to always identify a cause of death. For instance, the possibility to detect abnormalities of the distal Purkinje fibers network (Fig. 1.15) and their mechanistic role for reentry is out of our actual potential, to explain idiopathic ventricular SD in people with J wave at ECG [84].

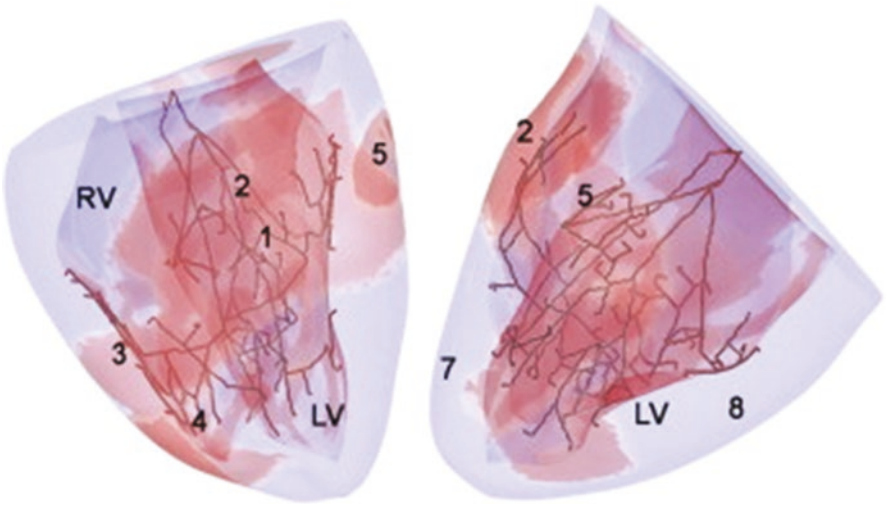

Fig. 1.15 Cardiac Purkinje cells in the subendocardium of the left ventricle. The network is a potential mechanism of reentry with the onset of tachyarrhythmia. At present, it is impossible to detect minimal injury with the current pathology methods of investigation

1.8 Role of Autopsy in Case of Sudden Death in Athletes

An autopsy is mandatory in case of SD and should be carried out according to guidelines [7]. Its role is to establish:

- Whether SD is attributable to natural or unnatural causes and, if natural, to cardiac or extracardiac diseases and to which mechanism
- If cardiac, the nosological identity and whether the mechanism has been arrhythmic or mechanical
- Whether the culprit disease is inherited, requiring molecular genetic screening in first degree relatives
- The need for toxicological analysis, if toxic or illicit drugs abuse are suspected

A thorough protocol of investigation should be followed in terms of gross, histologic, and, if necessary, ultrastructural investigations [7].

Study of the conduction system, by serial histologic sections technique, should be carried out only if ECG is available.

A molecular autopsy is fundamental in the setting of suspected viral myocarditis and genetically determined disease.

Toxicologic investigation, given to certified laboratories, is a complementary tool to be carried out in each young victim, particularly athletes [4, 5, 7]

In case of cardiac death, the best practice is to retain the entire heart specimen to be forwarded to specialized centers, after preliminary gross examination and photo documentation. According to guidelines, tissue-blood sampling should be stored in RNA later at 4 centigrade for nucleic acid extraction and then fixed in 10% formalin [7, 85].

In most SD cases, a cause can be easily found at autopsy by gross examination. However, we have to acknowledge that different degrees of certainty (certain, highly possible, and uncertain) do exist as far as the final cause is concerned.

For instance, acute thrombotic occlusion of a coronary artery, hemopericardium with cardiac tamponade, and pulmonary thromboembolism are to be considered as certain causes.

Coronary stenosis >75%, in the absence of any other explanation, should be regarded as highly probable, as well as the anomalous origin of a coronary artery from wrong right aortic sinus and ECG diagnosed ventricular preexcitation. On the contrary, other coronary artery anomalies like myocardial bridge or origin of the left circumflex branch from the right coronary artery should be regarded as an uncertain cause.

1.9 Toxicological Analysis

Forensic toxicology of the deceased is aimed at determining the presence of xenobiotics in liquids and tissues and evaluating the possible causal or co-causal role in the determination and dynamics of death. General recommendations on the sampling procedure can be found in numerous international publications [86, 87].

Although the toxicological protocol should be tailored to each case on the basis of circumstantial, clinical, and autopsy data, a minimum set of specimens should always be collected for forensic toxicology purposes, that is, at least two blood samples, preferably from a peripheral site, humor vitreous, urine, gastric contents, brain, liver and hair [86–88].

The ideal timing of collection is within 48 h since death. Ideally, medical examiners/forensic pathologists and toxicologists should discuss the case in advance of collection in order to ensure the most appropriate specimens are withdrawn [86–88].

All specimens, with the exception of keratinic matrices, should be frozen immediately after collection and stored at a temperature below −20 °C until analysis.

1.9.1 Sample Preparation

The isolation of substances from postmortem biological samples is often challenging, owing to the range of specimens encountered and their poor quality due to autolysis, putrefaction, or other postmortem changes. Liquid-liquid extraction under acidic, neutral, and basic conditions or solid phase extraction (SPE) for performing general unknown screening is used [89, 90].

1.9.2 General Unknown Screening

A systematic toxicological analysis (STA) traditionally includes gas chromatography (GC) and/or liquid-chromatography (LC) coupled to mass spectrometry to detect acidic, neutral, and basic compounds, with specific methods required for the

confirmation and quantification of drugs, drugs of abuse, and psychoactive substances. Ethanol and other volatiles are determined by head-space (HS)-GC on blood and fluids; immunoassay screening can be used for urine when available. More recently, chromatography coupled to high resolution-mass spectrometry (HRMS) has been applied for comprehensive, general unknown screening of xenobiotics, including pharmaceutical drugs, doping agents, chemicals, and houseware [89–92].

1.9.3 Interpretation of Results

When interpreting postmortem toxicology results, the possibility of changes in drug concentration after death because of degradation of the analyte, redistribution, autolysis, putrefaction, and/or analytical interference must be studied. Blood is certainly the most informative matrix because blood levels can be used to infer impairment or intoxication sometimes before death, but it is important to analyze multiple specimens and to compare the results. For instance, if drug concentrations are higher in the heart blood than in blood collected at peripheral sites, redistribution must be considered [89].

Moreover, there is no reliable or obvious correlation between concentrations measured in life and after death, and postmortem concentrations have often been overinterpreted in the past, particularly concerning "lethal concentrations" [93].

Several reference tables detailing therapeutic, toxic, and lethal concentrations of the most diffused xenobiotics have been published in monographs [91, 92] and evidence-based literature. Reference tables are useful when establishing a potential causative role of a specific molecule in a specific case, but they should be considered only the starting point of results interpretation. Xenobiotic stability, redistribution, individual pharmacokinetic and pharmacogenetic variability, comorbidities, or injuries, which could affect metabolism and tolerance, may hamper the interpretation of analytical results, making postmortem toxicology one of the most challenging subdisciplines within forensic toxicology. There is an absolute necessity of integrating all circumstantial, autopsy, histology, and histopathology data for a correct medico-legal and toxicological epicrisis, and for reconstructing the cause and mechanism of death.

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Electrocardiographic Changes in the Athlete's Heart

2

Massimiliano Bianco and Paolo Zeppilli

2.1 Introduction

Since the 1960s, the athlete's electrocardiogram (ECG) has attracted the attention of clinical cardiologists and sports doctors. Indeed, it is not uncommon to observe changes in the rhythm and morphology of its waves, due to remodeling of the heart by physical training [1], which make athlete's ECG "different" from what observed in a normal subject [1]. In the 1970s, some authors tried to use ECG changes to monitor the effects of the training itself [2], but this use has lost its charm, ever since more accurate methods are now available. Today, it is clear that changes once thought to be induced by training can also be found in healthy sedentary subjects. Finally, it is now well documented that some heart diseases, once unknown to sports physicians, can sometimes give rise to ECG tracings that are difficult to differentiate from those of athletes with definitely normal hearts [3].

The ECG is the simplest and cheapest exam we can use to identify disease at risk for sports-related sudden cardiac death (SCD) in the sports population. Aware of this, in the last 15 years, groups of experts tried to create criteria for appropriate ECG interpretation in athletes, with the last statement published in 2017 [4]. The problem of a correct ECG interpretation in athletes is even more demanding if we consider other aspects, such as age (junior/adolescent and masters athletes) and more recently ethnicity (just consider the plurality of races in professional sports teams of soccer, basketball, etc.).

As demonstrated by Corrado in Italy [5], the resting ECG can allow early identification of some heart diseases (cardiomyopathies, channelopathies) at risk of exercise SCD, with a favorable costs/benefits ratio [6, 7]. It is important to underline that

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Corrado's work has its roots in the fact that in Italy the recording of the ECG is an integral part of the pre-participation screening in competitive sport since 1982 [8]. For this reason, the knowledge of the typical ECG of the athlete's heart and of the characteristic ECG of heart diseases at risk must necessarily be part of the cultural background of every sports doctor. Quoting an editorial by Corrado and McKenna, the "appropriate interpretation of the athlete's electrocardiogram saves lives as well as money" [9].

2.2 The Athlete's ECG: General Considerations

While recording a resting ECG during the pre-participation screening for sports, we can observe changes in rhythm and different waves, with a prevalence that depends largely on gender, age and ethnicity of the examined subject, but most of all his/her *degree of training.* Regardless of the international protocols, we believe it is still useful from a practical point of view to simply classify the ECG changes of athletes in [8]:

- ***Physiological***, specifically related to physical training. They have definitely a good prognosis and may represent a problem only when erroneously interpreted as pathological.
- ***Borderline***, those changes which, even if totally or partially due to training, require a more careful evaluation, as they can also be the expression of underlying structural (cardiomyopathies) or functional (channelopathies) heart diseases. Marked sinus bradyarrhythmias, advanced atrioventricular blocks, and ventricular repolarization abnormalities (negative T waves) are included in this group.
- ***Abnormal or pathological***, which are not related to training and can be found in the general population with the same rate. We are dealing mainly with tachyarrhythmias (premature atrial and ventricular beats, atrial fibrillation, etc.), cardiac preexcitation, and major ventricular conduction delays (fascicular or bundle branch blocks, etc.).

For a correct interpretation of the physiological and borderline ECG changes, it is appropriate to premise ***two basic concepts*** (by many, but not all, considered obvious):

- *The ECG of an untrained or recreational sportsman/woman* must be considered in the same way as the tracing of a sedentary subject of the same age. Careful attention should be paid to not incur the mistake of considering all the anomalies as induced by training when this link does not exist.
- *When the ECG anomalies do not seem "appropriate"* to age, ethnicity, type, and/or intensity of training, a cardiac anomaly or definitely a disease (even though not necessarily at risk of SCD) should be suspected. For example, negative T waves can be the result of either an underlying heart disease with a good prognosis (mitral prolapse, minor forms of hypertrophic cardiomyopathy, etc.), drugs,

electrolyte imbalance, etc., that temporarily interfere with the electric activity of the heart, or genetic polymorphisms that influence cardiac morphology and function [10]. The successful identification of the actual cause of these ECG abnormalities depends on the medical knowledge and clinical experience of the physician, as well as on the diagnostic capability of the currently available imaging techniques.

2.3 Physiological Changes

Physiological changes are specifically related to physical training. They are routinely observed in high-level athletes engaged in regular training sessions for many years and usually disappear, in more or less time, with detraining. The following modifications are included in this group:

- *Sinus bradycardia*
- *PR interval prolongation (up to first-degree atrioventricular block)*
- *Isolated high QRS voltages*
- *Minor delay in right ventricular activation (incomplete right bundle branch block)*
- *Early repolarization*

Physiological changes, particularly when occurring simultaneously, characterize the typical athlete's ECG (Fig. 2.1a). A typical athlete's ECG, however, can be observed almost exclusively in aerobic, *endurance-trained athletes* (distance runners, cyclists, endurance skiers, rowers, etc.) and, less frequently, in athletes engaged in *aerobic-anaerobic sports activities* (soccer, rugby, water polo, etc.). This ECG pattern is usually associated with a significant morphological and functional cardiac remodeling (*athlete's heart*) and excellent aerobic power (VO_2 max). It is worth noting that in athletes, more than in sedentary subjects, the heart rate (HR) and rhythm, morphology, and duration of intervals (PR, QT) may be influenced by several factors, firstly the autonomic tone at the time of recording. So, it is advisable to record the ECG away from intense training sessions, preferably in the morning after a restful night's sleep, with the athlete lying in a supine position and in a quiet environment for at least 5–10 min.

Sinus bradycardia (HR < 60 beats per min, bpm) is definitely the most common finding. Its prevalence obviously depends on the type and intensity of training, being the rule in highly trained endurance athletes (100% of cases). The sinus rate is usually between 40 and 60 bpm (*mild-moderate bradycardia*), but a sinus rate <40 bpm (*marked bradycardia*) is not rare (Fig. 2.2a). In the youngest subjects, junior athletes, it is usually associated with respiratory sinus arrhythmia. A *wandering atrial pacemaker*, *junctional escape beats*, *and/or rhythms* can also be found, but less frequently than sinus bradycardia. In some high-level endurance athletes, the characteristic picture of *isorhythmic atrioventricular dissociation* can be observed. It is a slow junctional rhythm with narrow QRS complexes that alternates with a sinus rhythm of the same frequency (the P wave fluctuates in and out of the

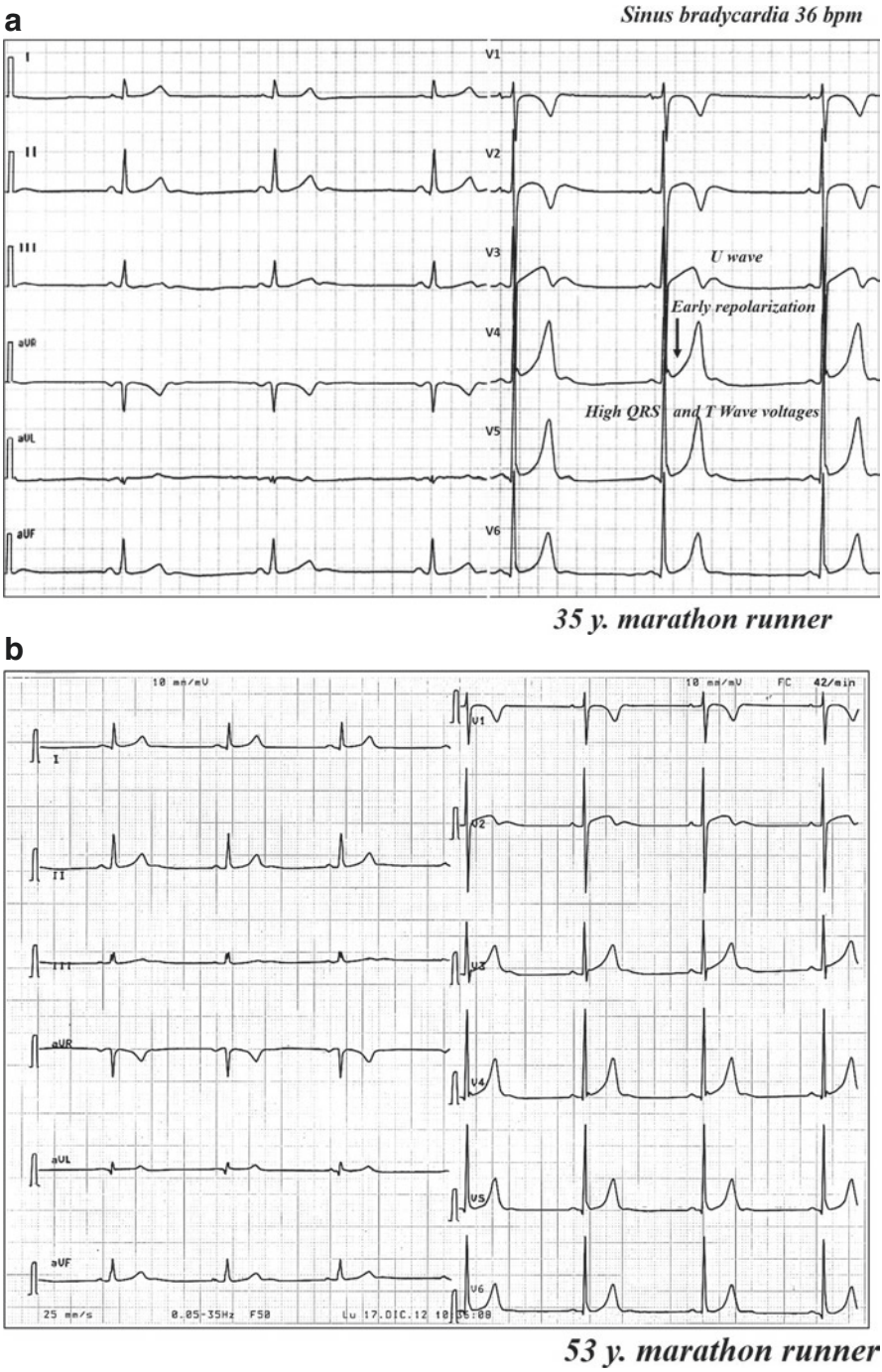

Fig. 2.1 (**a**) A 35-year-old, male, high-level marathon runner (maximum oxygen uptake 78 mL/kg/min) with a typical athlete's ECG (including negative T waves in right precordial leads). (**b**) The same athlete, who continued competing, at 53 years. Note the decrease in QRS voltages with the age

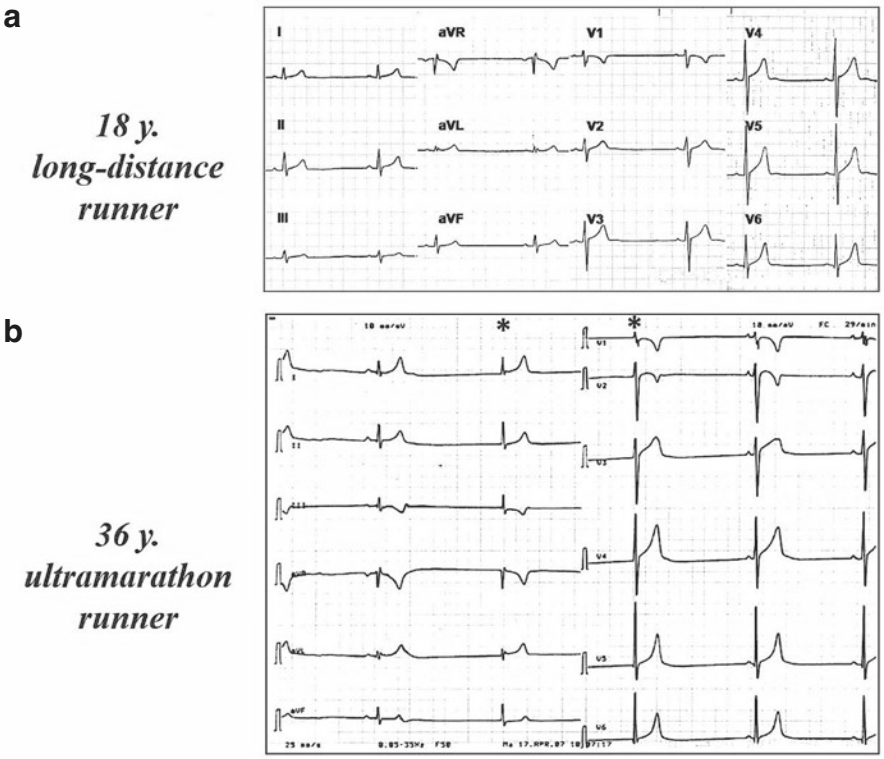

Fig. 2.2 (**a**) A 18-year-old, male, junior long-distance runner with physiological marked sinus bradycardia (35–37 bpm). (**b**) 18 years later, at the age of 36, after being several times world champion (and record holder) of the 100 km ultramarathon (maximum oxygen uptake 79 mL/kg/min). Note extreme sinus bradycardia (29 bpm) associated with junctional escape beats (asterisk) in the context of an isorhythmic atrioventricular dissociation (see text)

QRS complexes) (Fig. 2.2b). Sometimes, with a superficial reading, this picture may be misinterpreted as cardiac preexcitation, in which, however, the relationship between the P wave and the QRS complex is constant. All these physiological bradyarrhythmias disappear as the heart rate increases (orthostatic position, exercise, etc.) and exceptionally require further diagnostic evaluation.

First-degree atrioventricular block (AVB) (PR interval >0.20 s), although much less frequent than sinus bradycardia, can also be considered a physiological phenomenon, as its prevalence in well-trained athletes is tenfold higher than in sedentary subjects.

A *second-degree Mobitz type 1 AVB* (Wenckebach periodicity) is rather uncommon (in rest ECG), whereas an *advanced* or *complete AVB* is definitely unusual. Although their prevalence is higher in athletes than in sedentary people confirming a cause-effect relationship with training, they should be classified, more correctly, in the group of borderline changes.

Isolated high QRS voltages, particularly in the precordial leads, are also common. In the past, they were considered a reliable index of cardiac chamber enlargement. With the advent of echocardiography (ECHO), it has become clear that high QRS voltages are not always a sign of chambers enlargement and increased left ventricular mass. Several other factors may have a relevant effect on the ventriculogram, such as age, sex, body habitus (lean subjects), and ethnicity. High QRS voltages are frequently observed in the absence of any detectable increase in heart volume in young endurance-trained athletes. With advancing age, QRS voltages tend to decrease, and we must keep this in mind when master athletes are being examined (Fig. 2.1b). High QRS voltages are very common and frequently associated with negative T waves in Black athletes [11] (Fig. 2.3). All this explains the poor specificity of common QRS voltage criteria in the diagnosis of left ventricular hypertrophy, such as the Sokolow index [12]. Higher specificity can be achieved only by adopting more restrictive criteria, even at the expense of sensitivity.

Summarizing, the *isolated presence of high QRS voltages* suggestive of left (and right) ventricular hypertrophy can be considered a normal finding in athletes, especially Black. The additional presence of negative T waves, ST segment depression,

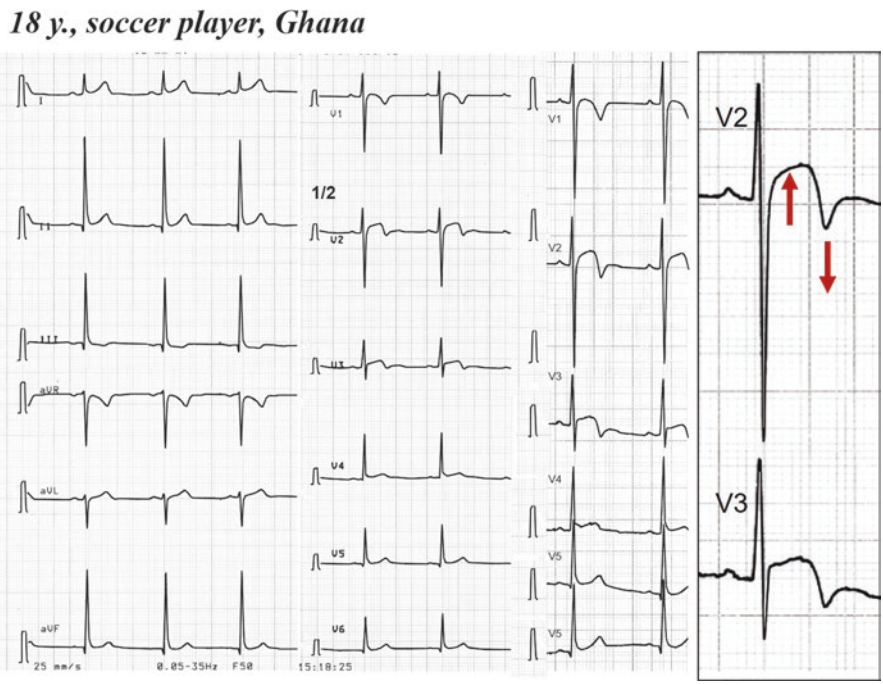

Fig. 2.3 Typical ECG tracing of a young Black professional soccer player from Ghana, with high QRS voltages (the automatized recording was at 5 mm/mV in precordial leads), elevated ST segment (in I, II, and from V2 to V6), and a terminal negative T wave in V2–V3 (better visible in the magnification of V2–V3)

or abnormal Q waves should raise the possibility of pathological hypertrophy and should prompt further evaluation.

In our experience, a mild increase in *QRS complex duration* can be detected only in endurance-trained athletes with a significant increase in ventricular dimensions and myocardial mass. *Minor delays in right ventricular activation* (incomplete right bundle branch block) have the same etiology and clinical significance. They are usually secondary to the physiological enlargement of the right ventricular cavity and, only exceptionally, are caused by a specific pathology (volume overload due to left-to-right shunt, arrhythmogenic right ventricular cardiomyopathy, etc.) [10].

Early repolarization (ER) is very common in athletes, especially males (Figs. 2.1 and 2.2) and Black (Fig. 2.3). Its prevalence varies among studies, reaching 80–90% in endurance-trained individuals, so this feature was considered an index of excellent aerobic power [13]. ER is defined *as the elevation of the QRS-ST junction (J-point) by ≥0.1 mV* often associated with a slurring or notching (J wave) of the terminal part of QRS. ER is usually present in the inferior and/or lateral leads [13, 14] and in athletes is more common in precordial leads where it can be an isolated finding. The ST segment elevation usually has an upward concavity and disappears during exercise.

Although the ER is considered a benign finding, it can rise diagnostic doubts when negative T waves are present, mimicking myocardial ischemia (uncommon in young athletes) or pericarditis (a possibility to be evaluated when chest pain and/or fever are present). Some years ago, the ER gained renewed interest first due to the "Brugada syndrome" and later for some "catastrophic" reports in which the ER was associated with an increased risk of idiopathic ventricular fibrillation [15, 16]. We believe it is necessary to point out that:

- An ST segment elevation is almost the rule in elite athletes (up to 90% in our experience), but it is also quite common in young active or sedentary subjects (30–40%) [17]. Elite athletes have a greater ST segment elevation, located more to the left in the precordial leads (V3–V5), and often associated with high QRS and T wave voltages.
- An ST segment elevation exclusively localized in right precordial leads (V1–V3) is detected in approximately 30% of elite athletes with ER. Of these, however, only 7–8% of them have a "coved" ST segment elevation, similar to what observed in type 1 Brugada pattern [17].
- Based on current evidence, when ER is isolated and without any clinical marker of pathology, it should be considered a benign variant in athletes [18, 19].

In healthy adults, T waves are positive in all ECG leads (except aVR and, sometimes, V1 and III). As previously mentioned, *tall positive T waves* (asymmetric, with the ascending limb having a more gradual slope than the descending one) are common in endurance athletes with marked sinus bradycardia, usually followed by clearly appreciable U waves (Fig. 2.1a).

On the other hand, Black athletes frequently show a J-point elevation and convex ST segment elevation in the anterior leads (V1–V4) followed by negative T waves

(Fig. 2.3). In the study of Papadakis [20], 13% of Black athletes showed isolated negative T waves from V1 to V4 compared with only 4% of Black sedentary controls. Most parts of these athletes had a J-point elevation and convex ST segment elevation associated with negative T waves. None of them had symptoms or signs of cardiomyopathy despite comprehensive evaluation and a 5-year follow-up period [20]. Moreover, similar findings have been described in female and adolescent Black athletes [21].

Based on these considerations, negative T waves in leads V1–V4 when associated with J-point elevation and convex ST segment elevation should be considered a normal feature of the "Black athlete's heart" (Fig. 2.3). In the absence of other clinical or ECG features of cardiomyopathy, they should not result in further investigations.

In addition, negative T waves confined to the anterior precordial leads (V1–V3) may be considered normal in adolescent athletes (*juvenile pattern*). Negative T waves in lead V1 to V3, however, have been observed in 10–15% of White athletes aged 12 years and only in 2.5% of those aged 14–15 years [22–24]. This feature seems to be more frequent in Black young athletes [25]. Even if the current guidelines state that negative T waves in V1–V3 can be considered normal in athletes aged <16 in the absence of symptoms, signs or a family history of cardiac disease [4], our experience suggests that it is quite uncommon to observe negative T waves beyond V3 in Caucasian athletes aged >14 or evidently postpubertal. In these few cases, serial ECGs recorded during adolescence may be useful to observe the progressive trend of T waves toward normalization. If this does not happen and/or if other "unusual" ECG signs are present (fragmented QRS, ventricular premature beats, etc.), we suggest further evaluation (ECHO first) for ruling out an arrhythmogenic, hypertrophic cardiomyopathy, or myocarditis (Fig. 2.4).

Although conflicting reports exist, the *QT interval duration* does not differ in athletes when compared to untrained subjects. In a study by our group [17] on healthy top-level athletes engaged in different sports, a long QT interval was documented in about 13% of subjects. With few exceptions, however, the QT interval was absolutely in the normal range when corrected for HR (QTc) by Bazett's formula. Such overestimation may derive from the difficulty in determining the end of the T wave, especially when is flat or deformed and prominent U waves are present. Especially at lower HR and when examining younger athletes, Fridericia's correction formula seems to be more useful [26].

In summary, top-level athletes engaged in aerobic or aerobic-anaerobic sports very frequently show physiological changes on their resting ECG, such as sinus bradycardia, PR interval prolongation or first-degree AVB, isolated high QRS voltages, ER, and minor delay in right ventricular activation.

Less frequently, negative/biphasic T waves can be observed in right precordial leads, usually associated with a significant right ventricular enlargement (Fig. 2.1). Such findings, if contemporary present, give origin to typical ECG tracings, which can be interpreted as "pathological" only by inexperienced observers.

Although rarely, the ECG of a top-level athlete may be so "atypical" to suggest an underlying structural heart disease. In such cases, an accurate reading of the ECG

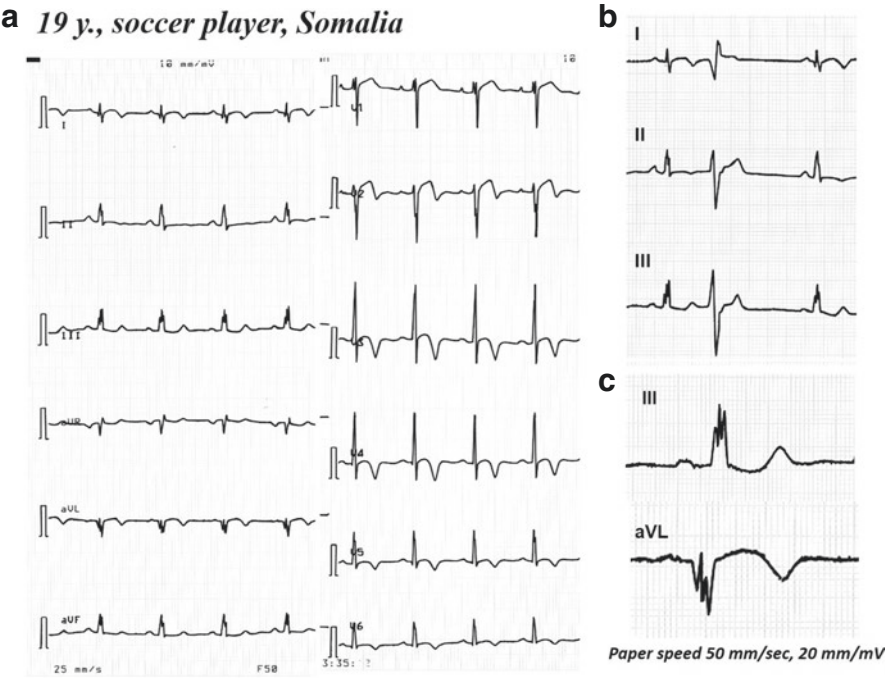

Fig. 2.4 ECG tracing of a young Black soccer player from Somalia, with a diagnosis of myocarditis (diffuse gadolinium late enhancement on MRI in the inferolateral wall of the left ventricle). (**a**) Negative T waves in precordial leads (erroneously interpreted as "black athlete's ECG), (**b**) premature ventricular beats, and (**c**) fragmented QRS complex in lead III and aVL (paper speed 50 mm/s, 20 mm/mV)

often allows to discover alterations that have been missed due to an incorrect or superficial interpretation, such as left or right atrial overload P waves, deep and tightened Q waves, left or right QRS axis deviation, etc. The identification of these anomalies may help the sports physician to make the correct diagnosis or suggest further investigations. Our experience suggests that *the first and most important test to do… is to compare the athlete's previous ECGs.*

2.4 Borderline Changes

We can define as *borderline* those ECG alterations that require a more accurate evaluation, because they can be related not only to training but also to a structural (cardiomyopathies) or functional (channelopathies) heart disease. In our opinion, marked sinus bradyarrhythmias, advanced AVBs, and ventricular repolarization abnormalities (negative T waves and ST segment depression) should be included in this group.

As for ***marked sinus bradyarrhythmias***, the type and degree of physical training as well as the presence of significant cardiac remodeling associated with high aerobic power are crucial in the clinical and prognostic evaluation process. For example, while we can still consider *extreme sinus bradycardia* (<30 bpm) as physiological in a top-ranking endurance athlete (Fig. 2.2b), we cannot do the same in sportspeople engaged in 2–3 training sessions per week, or having just begun their sports activity, or, even, practicing anaerobic (power) disciplines. Taking this in mind, we can also agree with the current guidelines including extreme sinus bradycardia among the pathological ECG findings [4].

Similarly, the presence of a ***second-degree Mobitz 1 AVB*** on rest ECG should be interpreted with caution. It can actually be present in highly trained athletes [27] but is very rare in young sportspeople [4, 10]. More advanced AVB (especially second-degree Mobitz type 2) are definitely uncommon and may suggest a degenerative or inflammatory disease of the AV node or of the whole conduction system. An accurate family history and ECG tracings of the closest relatives can be helpful. The presence of one or more relatives with an implanted pacemaker at a relatively young age and/or of others with bundle branch blocks suggests that such conduction disorders can be the initial expression of a Lenegre's disease that progressively worsens with the increase of age [28]. However, owing to their slow progression, these disorders are not an absolute contraindication to competitive sport, although require a careful follow-up.

Ventricular repolarization abnormalities (VRAs) require a few more lines. Since the 1970s, mounting evidence has shown that *intense training or overtraining* can modify the morphology and polarity of T waves [1, 2]. Over time, we have learned, however, that negative T waves, especially deep, in multiple leads is rare (3–4%) and cannot be "automatically" included in the physiological changes of the ECG. Our 40 years of experience (PZ) has taught us that negative T waves can be considered "normal" in elite athletes, especially Blacks, with significant or extreme hypertrophy (left ventricular wall thickness ≥13 mm), but only after having ruled out any cardiac anomaly or a "concealed" heart disease.

Sportspeople with negative T waves are often included in the so-called grey diagnostic zone [9, 29, 30] to exit from which knowledge, experience, patience, and sometimes a little luck are required. In these cases, it is advisable to make the athlete observe a period (2–3 months) of detraining. A reduction of the negative T wave component (rarely, its complete normalization!), however, can also be found in mild or segmental forms of hypertrophic cardiomyopathy (Fig. 2.5) [31, 32]. Conversely, a careful follow-up of athletes continuing their sports practice for several years (!), can make us reclassify T wave anomalies that were initially considered physiological or idiopathic (Fig. 2.6) [33, 34].

Even if some authors suggest to include left and right QRS axis deviation and left or right atrial overload P waves among borderline findings, the current evidence shows that right axis deviation and right atrial enlargement, especially when alone, can be considered normal variants, whereas left axis deviation and left atrial

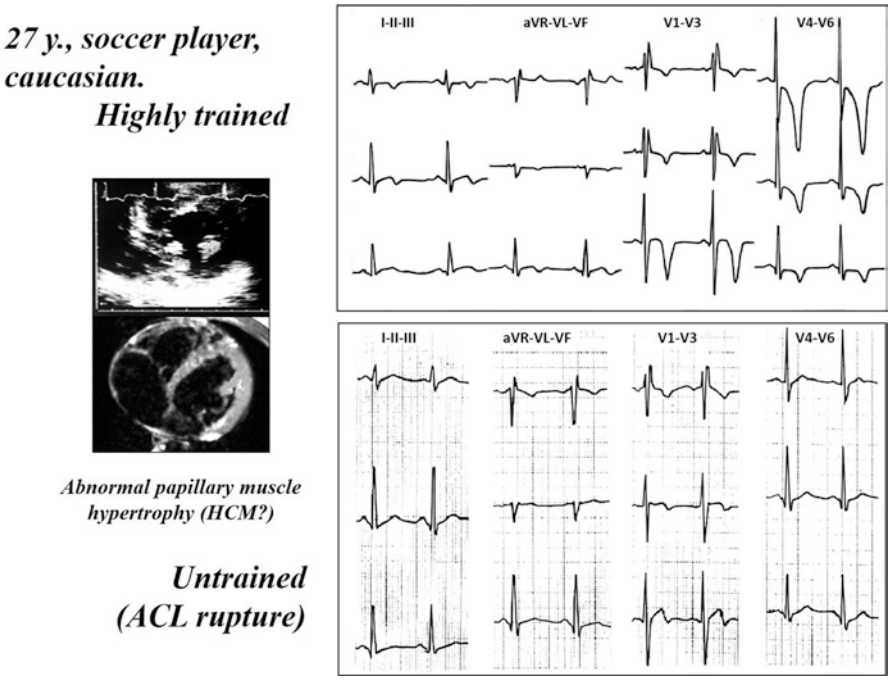

Fig. 2.5 A 27-year-old professional soccer player (Caucasian) with segmental hypertrophy of the papillary muscles at ECHO and MRI (a suspected initial form of hypertrophic cardiomyopathy). The ECG shows giant negative T waves in precordial leads. After 2 months of complete detraining due to an orthopedic injury (rupture of the anterior cruciate ligament, ACL), the ECG (lower panel) is completely different

enlargement may reflect an increase in left ventricular dimensions and mass in some athletes [4]. An aspect not to be overlooked in older athletes (masters).

Similar considerations should be made considering complete *right bundle branch block* (RBBB). The prevalence of RBBB ranges from 0.5 to 2.5% in athletic population [4, 35, 36]. Some athletes with RBBB may have a larger right ventricle without evidence of pathological structural cardiac disease. This suggested that RBBB may be a manifestation of more extreme right ventricular adaptation to exercise [37], even if we are not entirely convinced.

Summarizing, the borderline ECG patterns just described (marked sinus bradyarrhythmias and advanced AVB, VRAs, abnormal QRS axis deviation, left atrial overload, and complete RBBB), when isolated or associated with other physiological ECG changes, do not need further investigation in asymptomatic athletes without a family history of premature cardiac disease or SCD. On the other hand, the presence of more than one of these borderline findings in combination does warrant additional assessment.

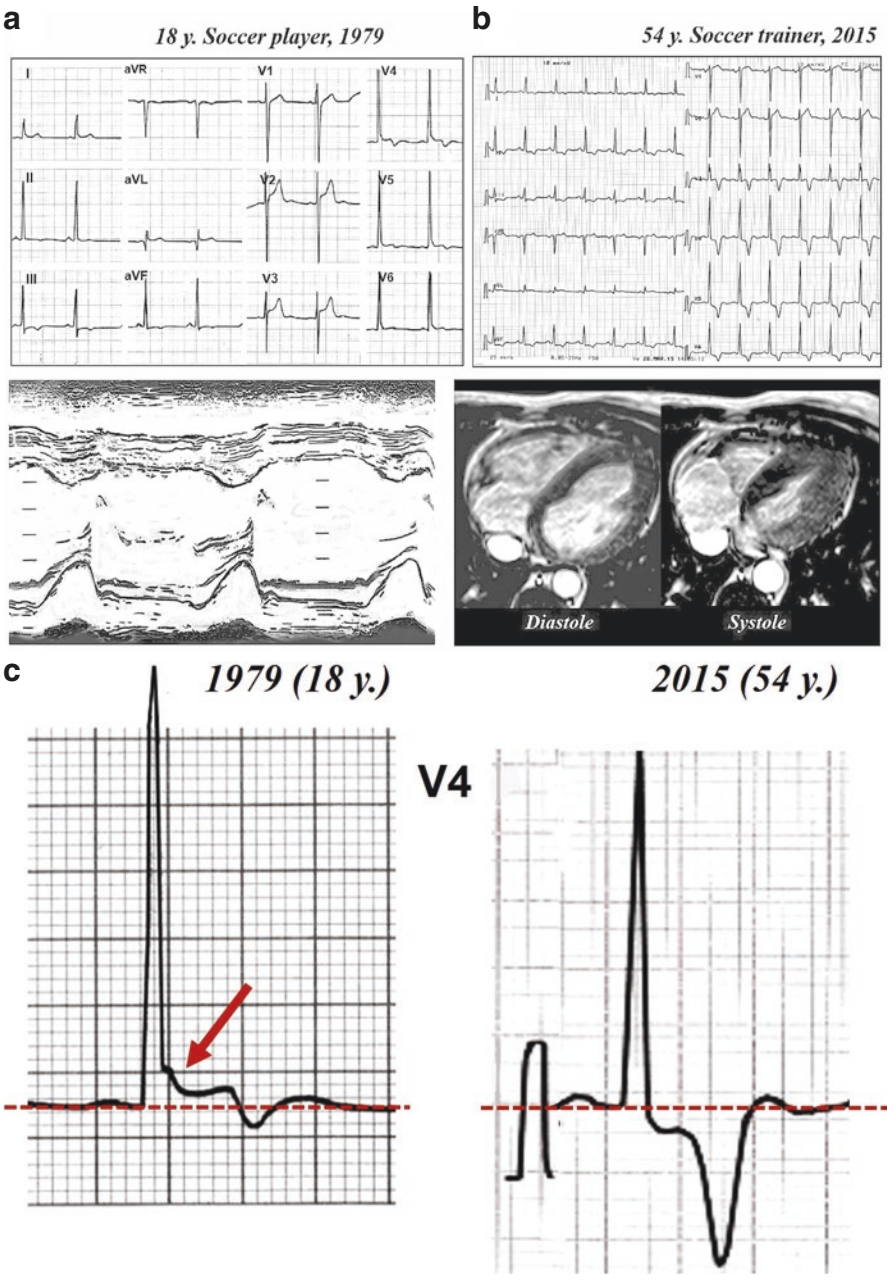

Fig. 2.6 (**a**) ECG of an 18-year-old high-level football player: high QRS voltages, negative/biphasic T waves in V4–V5, flat in V6. At that time, M-mode echocardiography showed moderate concentric left ventricular hypertrophy, interpreted as "athlete's heart." (**b**) ECG of the same subject at the age of 54 (now football coach). Deep negative T waves in the inferior and V3–V6 leads. Apical hypertrophic cardiomyopathy on MRI. (**c**) Magnification of lead V4 at the age of 18 and 54. Note that T wave inversion over time is associated with ST segment depression due to pathological increase in hypertrophy (late-onset apical hypertrophic cardiomyopathy)

2.5 Abnormal or Pathological Changes

Abnormal ECG findings more likely represent pathology rather than a normal response to training. They include deep negative T waves with ST segment depression, pathological Q waves, and complete left bundle branch block, which may suggest primitive or secondary cardiomyopathies as well as an ischemic heart disease. A long (more rarely short) QT interval and the ECG pattern of Brugada suggest a primary electrical disease (channelopathy). Finally, ventricular preexcitation, atrial tachyarrhythmias (supraventricular tachycardia, atrial fibrillation, and flutter), and ventricular tachyarrhythmias must be included in this group. They will be specifically addressed in the proper chapters of this book.

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Benign Arrhythmias and Conduction Defects in Athletes

3

Alessandro Biffi, Stefano Palermi, Alessandro Serio, Eleonora Murazzi, and Felice Sirico

3.1 Sinus Arrhythmia

3.1.1 Definition

Sinus arrhythmia is a physiological phenomenon, common in young people and related with breathing phases that cyclically change the neuro-autonomic balance of heart rhythm [1]: inspiration stimulates the sympathetic system and sinus tachycardia, while expiration stimulates the parasympathetic system and sinus bradycardia.

3.1.2 Epidemiology in Sport

Sinus arrhythmia is a consequence of an increased vagal tone [2, 3]: the P wave axis remains normal in the frontal plane and the heart rate fluctuation should resolve with the onset of physical activity or with administration of atropine [4]. Therefore, sinus arrhythmia should be considered a normal finding in athlete's ECG [2]. The physiologic mechanisms by which training may induce these intrinsic changes in the specialized conduction system of the heart are unknown and may be multifactorial [5]: an altered ionic balance across the membrane [6] as well as biochemical and mechanical effects induced by dilation and hypertrophy [7] has been proposed as possible explanations.

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3.1.3 Current Guidelines

According to current guidelines [8, 9]:

– athletes with sinus arrhythmia without symptoms can participate in all competitive athletic activities unless otherwise excluded by underlying structural heart disease or other arrhythmias.

3.2 Sinus Bradycardia

3.2.1 Definition

Sinus bradycardia is defined as a sinus rhythm with a resting heart rate <60 bpm [10].

3.2.2 Epidemiology in Sport

Moderate and asymptomatic sinus bradycardia (40–50 bpm) is one of the most common finding in sport practitioners [11], and it reflects both functional and structural adaptations [12, 13]. Its prevalence varies widely among the populations, oscillating from 4 to 8% in non-athletes, and from 40 to 90% in athletes [14]. In the absence of symptoms such as fatigue, dizziness, or syncope, heart rates ≥30 bpm are considered a normal finding in highly trained athletes. Sinus pauses >2 s during 24-h Holter ECG monitoring are also quite common in athletes and are observed in more than one-third of them [11]. Sinus bradycardia should resolve with the onset of physical activity [2, 4]. Sinus bradycardia may be attributed to increased vagal tone and receptor density reduction, especially in the inferior left ventricular wall [15, 16]. Additional mechanisms have been described, such as reduced sensitivity to catecholamines, altered neural input to the sinus node, carotid bulb and left ventricular baroreceptor stimulation due to greater contractile force, and increased afferent vagal reflex with acetylcholine release and blockade of adrenaline release [17]. However, electrophysiological studies performed in athletes and sedentary subjects with sympathetic and parasympathetic blockade showed the existence of non-autonomic influences in the athletes sinus bradycardia at rest [5]. Nevertheless, recent evidences showed that vagal hypertonia is not the main mechanism behind this physiological adaptation, but rather intrinsic structural and ionic channel remodeling of the sinus node [18–20]. Some athletes may have extreme forms of sinus bradycardia, such as a resting sinus rhythm <30 bpm or heart pauses ≥3 s [2].

Clinical evaluation includes a careful history to determine whether sinus bradycardia is related to symptoms like dizziness or syncope. Exercise stress test may be useful to verify a normal heart rate response. Symptomatic athletes and asymptomatic athletes with extreme bradycardia at rest (e.g., <30 bpm on ECG) should have 24-h Holter ECG monitoring and a cardiac work-up to exclude structural heart disease [12, 21]. Even if in a small percentage of sport practitioners, sinus bradycardia

is a negative prognostic sign [22]. According to several authors, in the absence of symptoms and evidence of structural cardiac disease and adequate chronotropic response to physical exercise, these athletes should not be excluded from their usual sporting activities [2]. However, the tolerable limit of pause duration to define sports interruption, or even pacemaker implantation, is not well established [23]. Cessation of sports activity may result in resolution of symptoms and improvement in rhythm after 3–6 months [24]. In asymptomatic patients with extreme bradycardia at rest (e.g., <30 bpm on ECG) a yearly follow-up could be sufficient. In those who were symptomatic before but became asymptomatic after a detraining period, a follow-up evaluation after 6 months is recommended [12].

With significant sinus bradycardia, a junctional or ventricular escape rhythm can compete with the sinus rhythm. Sinus arrhythmia and wandering atrial pacemaker are also more prevalent in athletes compared with the general population [25].

3.2.3 Current Guidelines

According to current guidelines [8, 9, 12]:

Eligibility for competitive sport can be granted in case of sinus bradycardia, if:

- absence of underlying cardiac disease that is incompatible with sports
- absence of bradycardia-related symptoms (syncope, asthenia, dizziness, dyspnea, effort intolerance)
- in subjects with no evidences of sinus node intrinsic dysfunction (at least 85% of max heart rate expected at exercise stress test and no heart pauses >3 s at 24-h Holter ECG)
- in highly trained aerobic athletes, also having <40 bpm and heart pauses >3 s
- in doubtful cases, after a detraining period (3–6 months) leading to a disappear of these phenomena

Athletes should be restricted from training and athletic competition while being evaluated (exercise stress test and 24-h Holter ECG). If treatment of the bradycardia eliminates symptoms, they can return to sport.

3.3 Right Bundle Branch Block

3.3.1 Definition

Right bundle branch block (RBBB) is divided into two subtypes [26]:

- complete RBBB: QRS complex >120 ms + rsR' pattern in leads V1 and/or V2 or RR' pattern in leads V1 and/or V2 + wide and slurred S wave in lead V6 and I (S > R duration or S wave duration >0.06 s)
- incomplete RBBB: QRS complex 100–120 ms + rsr' pattern in leads V1 and/or V2.

3.3.2 Epidemiology in Sport

Mildly delayed right ventricle conduction in trained athletes could be linked to a spectrum of structural and physiological cardiac remodeling (i.e., right ventricle dilatation, increased cavity size, and resultant increased conduction time [13, 27]); indeed, some highly trained athletes manifested a reduction in right ventricular systolic function at rest and a higher rate of RBBB [28]. Therefore, incomplete RBBB represents a phenotype of cardiac adaptation to exercise [13], and in the absence of other features suggestive of disease does not require further evaluation [2]. Its prevalence in athletes varies between 35 and 50% [9]. Complete RBBB is detected in approximately 1% of the general population, with a range of 0.5–2.5% in several studies [29–31]. The presence of at least one of other borderline findings (left axis deviation, left atrial enlargement, right axis deviation, right atrial enlargement) does not warrant further assessment in asymptomatic athletes without a family history of premature cardiac disease or sudden cardiac death. Conversely, the presence of more than one of these borderline findings in combination should be additionally investigated [2].

3.3.3 Current Guidelines

According to current guidelines [8, 9]:

Eligibility for competitive sport can be granted in:

- absence of underlying cardiac disease that is incompatible with sports
- isolated RBBB
- RBBB + left anterior fascicular (LAFB) or posterior fascicular (LPFB) blocks only after excluding cardiac diseases

In particular, athletes with RBBB, who do not develop periods of second degree Mobitz 2 AV block or third degree AV block spontaneously or during exercise and who have no symptoms or heart disease identified by appropriate testing that otherwise precludes participation, can participate in all competitive athletics.

Eligibility for competitive sport should be denied in:

- presence of family history of sudden cardiac death
- presence of cardiac syncope
- presence of family history of Lenegre disease, Brugada syndrome, or ion channel diseases

3.4 Left Bundle Branch Block

3.4.1 Definition

Left bundle branch block (LBBB) is an electrocardiographic abnormality detected in patients affected by abnormal cardiac conduction through anterior and posterior left fascicles of the His-Purkinje system [32].

3.4.2 Epidemiology in Sport

LBBB is found in less than 1% athletes [28, 33]. On the other hand, there is a high rate of cardiomyopathy in patients with LBBB: one study comparing athletes and patients with hypertrophic cardiomyopathy showed that 5.9% of these patients had LBBB, but no athlete with normal cardiac imaging had LBBB [34]. Thus, complete LBBB always should be considered an abnormal finding and requires a comprehensive evaluation to rule out a pathological cardiac disorder [2].

3.4.3 Current Guidelines

According to current guidelines [8, 9]:

Eligibility for competitive sport can be granted in:

- absence of underlying cardiac disease that is incompatible with sports
- isolated LAFB or LPFB
- LBBB, RBBB + left anterior fascicular (LAFB), or posterior fascicular (LPFB) blocks only after excluding cardiac diseases.

In particular, athletes with permanent or rate-dependent LBBB who do not develop spontaneous second degree Mobitz 2 AV block or third degree AV block and who have no symptoms or heart disease identified by appropriate testing that otherwise precludes participation can participate in all competitive athletics.

Eligibility for competitive sport should be denied in:

- presence of family history of sudden cardiac death
- presence of cardiac syncope
- presence of family history of Lenegre disease, Brugada syndrome, or ion channel diseases.

In athletes with concerning symptoms, an electrophysiological study (EPS) is recommended. An athlete with a normal H-V interval (time from the initial deflection of the His bundle potential and the onset of ventricular activity) and a normal atrio-ventricular (AV) conduction response to pacing can participate in all competitive sports unless otherwise restricted by their structural heart disease; athletes with abnormal AV conduction characterized by an H-V interval >90 ms or a His-Purkinje block should have pacemaker implantation.

3.5 Atrio-Ventricular Blocks

3.5.1 Definition

Atrio-ventricular blocks (AV blocks) are partial or complete interruptions of the transmission of the electrical impulse from the atrial chambers to the ventricular ones [35].

3.5.2 Epidemiology in Sport

AV conduction disorders are frequent in athletes: first degree AV block is the most common finding (from 7–10% of basal ECG, up to 25.7–40% of 24 h Holter ECG [3, 36]), followed by second degree Mobitz 1 AV block (15–22% of basal ECG [37]). Both are due to parasympathetic hypertonia and are common in endurance athletes [4], being part of physiological adaptations to exercise [13, 38]: in trained athletes indeed, there is a sympathetic decrease with relative vagal tone prevalence, and a concurrent decrease of the heart rate [2, 39]. In asymptomatic athletes, the resolution of this arrhythmia through hyperventilation or physical exercise confirms their functional origin and excludes any pathological meanings [40]. If PR interval does not shorten with physical exercise, is associated with syncopal symptoms or with a familiarity for cardiac pathology, it is advisable to perform an echocardiogram and a 24-hours Holter ECG [2]. Most of the first degree AV blocks show a PR interval $\leq$280 ms [24]; a PR interval $\geq$400 ms has to be considered significantly prolonged and therefore must necessarily be investigated [2]. More severe AV blocks are rare. Second degree Mobitz 2 AV block or third degree AV block may be present in some elite athletes, especially at night (24-h Holter ECG): their persistence during routinely ECG and their failure to disappear during exercise should be investigated to exclude heart diseases [12, 41]. However, ventricular pauses of $\geq$3 s or a resting heart rate $\leq$40 bpm due to conduction disturbances are rarely observed in leisure-time athletes, even if such disturbances have been reported in high-level athletes [42]. Therefore, these arrhythmias should never be considered as benign findings in the athlete's ECG, and should necessarily be investigated [2, 43]. Electrophysiological study is advisable in case of second or third degree AV blocks. In doubtful cases, a period of detraining (3–6 months) and a subsequent revaluation are recommended [9, 12, 39].

3.5.3 Current Guidelines

According to current guidelines [5, 9, 12]:

- athletes with asymptomatic first degree AV block or second degree Mobitz 1 AV block at rest and normalization during exercise or hyperventilation can participate in all sports.
- symptomatic athletes with second degree Mobitz 2 AV block while awake should temporarily refrain from sports. If exclusion of a structural cause and normalization within 3 months occurs, low-moderate sports can be resumed. After 4 weeks with tolerable low-moderate sports, higher intensity sports may be undertaken. Follow-up with 24-h Holter ECG is advised.
- in athletes with extreme PR prolongation first degree AV block (>300 ms), more intensified follow-up is warranted (e.g., every 6 months).
- second degree Mobitz 2 AV block or third degree AV block requires exclusion of underlying structural heart disease,

– in second degree Mobitz 2 AV block or third degree AV block without structural heart disease, a deconditioning phase of 3–6 months can be considered,
– in second degree Mobitz 2 AV block or third degree AV block with structural heart disease, a pacemaker is recommended,
– eligibility for low intensity sport can be considered in congenital AV block with narrow QRS interval, with resting heart rate >40 bpm that increase during physical activity and without effort's complex ventricular arrhythmias,
– eligibility for competitive sport should be denied in case of symptomatic bradycardia, presence of cardiac disease that is incompatible with sports and pauses >3 s (except trained athletes practicing aerobic sports).

3.6 Premature Ventricular Beats

3.6.1 Definition

A premature ventricular beat (PVB) is an extra, abnormal heartbeat, that is electrocardiographically characterized by an early onset and a morphologically abnormal QRS complex with a duration >120 ms [44, 45].

3.6.2 Epidemiology in Athletes

Even if there is a traditional perspective that PVBs are a consequence of the structural and neuro-autonomic remodeling of the athlete's heart [46], ventricular arrhythmias rate in young competitive athletes is low, similar to that of sedentary individuals and it is unrelated to type and intensity of sport practiced. Young athletes were found to be more likely to have isolated PVBs, compared with their sedentary counterparts (49% vs 28%) [47], but this difference was not seen in a study of middle-aged athletes and sedentary controls (53% vs 50%) [48]. PVBs at resting ECGs are uncommon: multiple PVBs can be found in less than 1.1–2.1%, and polymorphic PVBs only in 0.1% [31, 49]. Similar to the non-athletic general population, PVBs in the athletes may be associated with an underlying myocardial substrate, potentially at risk of sudden cardiac death. Therefore, the first objective in evaluating an athlete with ventricular arrhythmias is to exclude life-threatening cardiovascular diseases [50].

According to the number, morphologic pattern, complexity, response to exercise and clinical manifestation, PVBs can be classified as common and likely benign or uncommon and potentially malignant because of underlying cardiac pathology [50, 51]. A multiparametric approach is useful for differentiating between these two variants. Different studies have shown evidence that up to 30% of athletes with ≥2000 PBVs per 24 h [52], were found to have underlying structural heart disease [46, 53]. However, a high number of PVBs in itself does not confer an increased risk of malignant events [51]. For this reason, additional tests are necessary in athletes with ≥2000 PBCs per 24 h, or with episodes of non-sustained ventricular

tachycardia, or with an increasing burden of PVBs during an exercise test. These additional evaluations include echocardiography, cardiac magnetic resonance imaging (MRI), and electrophysiology study.

Further evaluation is warranted when ≥2 PVBs are recorded on a resting 12-lead ECG [2]. However, even a single PVB may deserve attention especially in the presence of one or more of these five features: (1) positive family history of premature sudden cardiac death (SCD) or cardiomyopathy, (2) relevant symptoms, (3) associated ECG abnormalities, (4) uncommon PVB morphology, and (5) short coupling interval [54]. Work-up should also include a search for agents that may enhance electrical ventricular irritability, such as the use of excessive amount of alcohol, illicit drugs, or stimulants, particularly ephedrine and caffeine [25].

The assessment of the morphology of the ectopic QRS complex on the ECG helps to identify the anatomical origin of the PVBs [54]: common patterns in athletes are infundibular and fascicular ones, while atypical RBBB with QRS ≥130 ms and LBBB patterns with superior or intermediate axis are not common and should be further investigated. The prevalence of concomitant repolarization/depolarization ECG abnormalities increases the probability of an associated disease [25]. An increase in the arrhythmia at the beginning of exercise, disappearance at peak exercise, and reappearance during recovery usually suggest a benign process [46]: exercise stress test should not be stopped at the 85% of theoretical maximal heart rate but continued until the athlete is exhausted in order to increase the test sensitivity [51, 55].

3.6.3 Current Guidelines

According to current guidelines [9, 51, 56]:

- athletes with ≥2 PVBs on a baseline ECG (or ≥1 PVB in case of high-endurance athletes, or positive family history of premature SCD or cardiomyopathy, relevant symptoms, associated ECG abnormalities, uncommon PVB morphology, and/or short coupling interval) should undergo a complete evaluation to exclude underlying structural or arrhythmogenic conditions. This includes a detailed familial history, ECG (morphology suggestive of common and likely benign, or uncommon and potentially malignant VPB forms), 24-h Holter ECG monitoring possibly with a 12-lead system and including a sports session (morphology, number, and complexity of VBPs), exercise stress test (increase or decrease with exertion), and suitable imaging (echocardiography and computerized tomography and/or MRI). If no indication of familiar or structural underlying disease, all competitive and leisure-time sports activities are allowed.
- athletes with a high prevalence of asymptomatic PVBs (in absence of structural heart disease) should be re-evaluated annually (particularly in case of children and adolescents) in order to identify potential changes in the arrhythmic burden and in underlying cardiac condition. In symptomatic athletes without structural heart disease, medical treatment for PVB may be an option.

– eligibility for competitive sport can be granted in case of absence of sudden cardiac death or arrhythmia family history, absence of cardiac diseases, absence of symptoms (syncope, dizziness, palpitations), in subjects with benign pattern such as fascicular or outflow tract origins.
– eligibility for competitive sport should be denied in case of presence of sudden cardiac death or arrhythmia family history, presence of cardiac diseases not compatible with sport, presence of symptoms (syncope, dizziness, palpitations), PVBs premature and/or repetitive with short couples and/or non-sustained ventricular tachycardia, frequents PVBs with concomitant reduction of ejection fraction.

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Hypertrophic Cardiomyopathy and Left Ventricular Non-Compaction

4

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4.1 Text

Hypertrophic cardiomyopathy (HCM) is a myocardial disease mostly caused by variants in genes encoding sarcomeric contractile proteins. It is diagnosed when left ventricular (LV) wall thickness exceeds 15 mm in the absence of a cardiac or systemic disease capable of inducing the same magnitude of LV hypertrophy [1–3].

HCM is of special interest because it is considered one of the causes of exercise-related sudden death/cardiac arrest (SD/CA) in competitive athletes. Estimates of the proportion of SD in competitive athletes attributable to HCM vary widely. Early evidence showed HCM was a frequent cause of SD in young athletes [4]. Consequently, conservative exercise recommendations were issued, restricting all athletes with HCM from competitive sports [4, 5]. Indeed, Maron et al., in a large registry including a total of 1866 athletes (age: 19 ± 6 years) who died suddenly or survived after CA in the United States from 1980 to 2006, found that SD were predominantly due to cardiovascular disease (n = 1049, 56%), with the most common causes being HCM (36%) and congenital coronary artery anomalies (17%) [6]. Similar results were also reported in subsequent studies analyzing databases (including autopsy reports) from national registries of SD in athletes [7]. Moreover, prospective surveillance was conducted over 4 years in the United States reviewing autopsy reports, death certificates, and medical

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records [8]: common causes of SD/CA included HCM (20.6%), idiopathic left ventricular hypertrophy (LVH) (13.4%), and coronary artery anomalies (12.0%) [8].

However, in a more recent autopsy-based study, Harmon et al. demonstrated a lower incidence of SD related to HCM, with only 8% of SD due to HCM and 8% due to idiopathic LVH/possible cardiomyopathy, while the most common findings were autopsy-negative unexplained SD [9].

Finocchiaro et al. analyzed 357 athletes who died suddenly between 1994 and 2014, with detailed postmortem evaluation, including histological analysis by an expert cardiac pathologist. Arrhythmic SD syndrome was the most prevalent cause of death, and only 23 (6%) were due to HCM [10]. HCM was diagnosed in 6% of athletes <18 years of age, 8% of those 18–35 years of age, and 5% of those >35 years of age. Idiopathic LVH/fibrosis was identified as a cause of SD in 10%, 14%, and 26% of individuals with <18, 18–35, or >35 years of age, respectively [10]. Notably, 10/23 SD in the HCM cohort occurred at rest and only 13/20 during exercise [10]. Similarly, in a prospective population study of 490 SD cases in the young (aged 1–35 years), 40% of death were found to be unexplained, and HCM accounted for only 4% of SD cases, with only 30% of cases of SD occurring during or immediately after exercise [11].

Therefore, the close association of exercise and SD due to HCM is currently under debate. Lampert et al. reported that individuals with HCM who continued participating in sports after implantable cardioverter-defibrillator (ICD) implantation did not reveal an increased number of shocks during exercise [12, 13]. Pelliccia et al. observed the clinical outcome of 35 HCM athletes, engaged in training and competitions for 5–31 years. Over a mean 9-year follow-up, the incidence of event/symptoms was not different among individuals who suspended regular exercise versus those who continued sport programs. Only one CA occurred and was not related to exercise [14]. Recently, Pelliccia et al. in a larger cohort of 88 athletes with HCM, who were followed up for a 7-year period, confirmed that the incidence of symptoms or major events was not different in those that quitted exercise vs. those who remained engaged in competitive sport [15]. In addition, SD from HCM has been recently reported occurring mostly during rest or usual life activities rather than during exercise or during emotional stress [16, 17]. Moreover, in a cross-sectional study on 187 patients with HCM, vigorous exercise correlated with favorable diastolic function and larger LV volumes and was not associated with an increase of ventricular arrhythmias [18]. Similarly, larger LV cavities, normal indices of diastolic function, and less LV hypertrophy have been found in athletes with HCM compared with sedentary HCM patients [19].

Although a level of uncertainty still exists regarding the long-term safety of exercise at different levels of intensity and training in HCM patients, there is limited evidence to indicate that all individuals with HCM are vulnerable to fatal arrhythmias during exercise [13]. Therefore, a systematic approach for risk stratification is required when assessing an individual with HCM who requests exercise advice [13].

4.2 Risk Stratification in Athletes with Hypertrophic Cardiomyopathy

Risk stratification in competitive athletes with HCM is challenging, due to the lack of prospective studies reporting the disease progression pattern and SD in patients engaging in regular, intensive exercise [3, 13]. Moreover, in adult HCM patients, myocardial ischemia has been shown to occur at different heart rate levels by atrial pacing [20]. Myocardial global hypoperfusion assessed by positron emission tomography (PET) is associated with worse outcome and adverse LV remodeling, but not SD [21, 22]. However, while in clinical practice the "ischemia" threshold is difficult to assess with current noninvasive techniques and represents a major limitation to the identification of high-risk HCM patients, both congenital coronary artery anomaly, myocardial bridging, tunneled LAD, and associated atherosclerotic coronary disease should be ruled out by CT coronary angiography scan [21, 23, 24].

The baseline evaluation should include a comprehensive personal and family history with consideration of the age of the individual and years of exercise prior to diagnosis, assessment of the phenotype severity, and the presence of any conventional risk factors for SD/CA [3, 13].

Age is a relevant risk determinant. The mean age of death in the largest series of SD from the United States was 18 years, with 65% of deaths occurring in athletes ≤17 years [6, 13]. A higher incidence of SD/CA has been demonstrated in male, African-American Black and young athletes [7–9]. Participation in high-intensity competitive sports itself has been considered as a potential independent risk factor for SD/CA, due to accompanying alterations in hydration, electrolyte, and acid-base status and surges in catecholamine levels [3, 25]. Highly-dynamic, intermittent sport disciplines, such as basketball and football, demonstrated the highest risk of SD [3, 8, 26, 27]. Furthermore, individuals with a history of CA or sustained (>30 s or associated with hemodynamic compromise) ventricular arrhythmias or unheralded syncope and individuals with exercise-induced symptoms should be considered at high-risk [1, 13, 28].

Ventricular and supraventricular arrhythmias assessment by standard 12-lead ECG and ambulatory ECG monitoring is recommended for risk stratification; asymptomatic non-sustained ventricular tachycardia (NSVT) confers considerable risk of SD in younger individuals (≤35 years) [1, 13, 29].

All individuals should be evaluated by echocardiography, considering that parameters such as LV wall thickness, left atrial size, and LV outflow tract (LVOT) gradient (e.g., assessed at rest, during Valsalva or even better during and after exercise by Echocardiography) have been associated with an increased risk of SD according to contemporary guidelines [1, 13, 28–30].

By exercise test or cardiopulmonary exercise test (CPET) functional capacity, an abnormal blood pressure response to exercise (by progressive hypotension or a failure to increase the systolic blood pressure >20 mm Hg) and exercise-induced symptoms or arrhythmias represent additional marker of risk in HCM patients [28, 31].

Cardiac magnetic resonance (CMR) with high spatial resolution and fully tomographic imaging of the heart, as well as assessment of myocardial fibrosis by late

gadolinium enhancement (LGE), is an important imaging technique for assessing the risk [2]. In fact, LGE (i.e., myocardial fibrosis) represents a noninvasive marker for increased risk due to potentially life-threatening ventricular tachyarrhythmias [2]. Risk of SD is significantly associated with both the presence and the extent of LGE, with LGE ≥15% of LV mass showing an increase in arrhythmic risk also in those patients otherwise considered to be at lower risk [32, 33]. Unfortunately, precise calculation of LGE volume by current CMR software has several limitations.

Also the absence of atrial natriuretic peptides (proBNP or BNP) and troponin level abnormalities may be helpful to identify low-risk patients.

HCM risk-SD score has been developed to construct three categories of risk (high, intermediate, and low), using predictor variables that have been associated with an increased risk of SD in HCM patients [1, 28]. Unfortunately, it relies on evidence derived from predominantly nonathletic cohorts and does not take into account the risk of SD related to hemodynamic and metabolic stresses of high-intensity exercise [13, 28].

In summary, the most recent European [13] and AHA [2] guidelines affirm that the beneficial effects of exercise on general health can be extended to patients with HCM, as healthy recreational exercise of low-moderate intensity has not been associated with an increased risk of ventricular arrhythmic events in recent studies. They suggest the criteria to define a relative "low-risk" patient and support a more liberal approach to sports participation in these individuals after careful evaluation (Fig. 4.1). It is indisputable, however, that the absence of all major risk factors does not convey immunity to SD, and even patients with low risk may

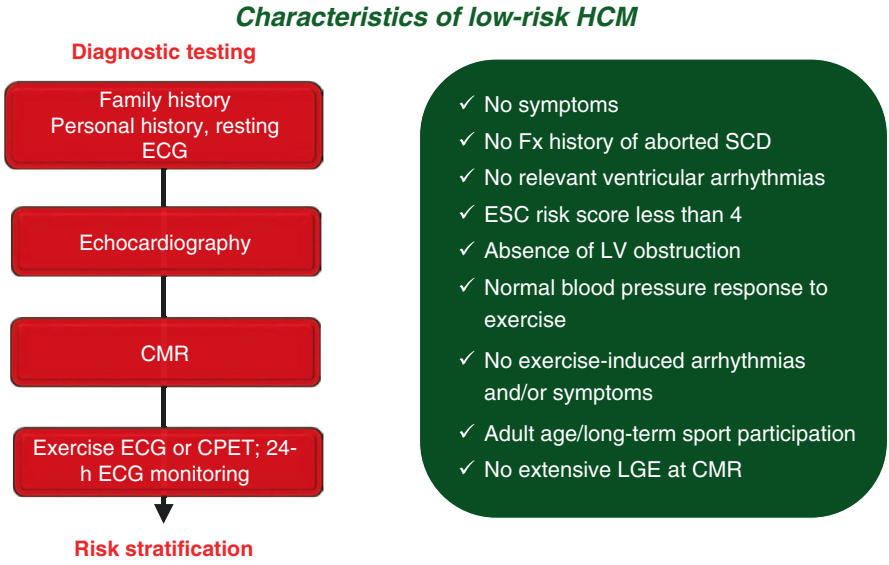

Fig. 4.1 Scheme of the essential diagnostic testing commonly used in clinical practice for risk stratification in HCM patients and derived criteria to define low-risk category [13]. *LGE* late gadolinium enhancement, *CMR* cardiac magnetic resonance, *CPET* cardiopulmonary exercise test

die suddenly [13]. HCM patients should be advised during a shared decision-making process [3, 13]. Notably, while the indication to practice competitive sports is still debated even in low-risk HCM patients, they may benefit from practicing moderate-intensity aerobic exercise that should be prescribed with a tailored individual approach [34].

4.3 Left Ventricular Non-Compaction Cardiomyopathy

Left ventricular non-compaction (LVNC) is a myocardial disorder phenotypically characterized by increased trabeculation of LV chamber, typically two-layered myocardium with a thin subepicardial compacted layer and a non-compacted thicker hypertrabeculated layer [35, 36]. Athletes often show LV hypertrabeculation that may mimic LVNC. Up to 8% fulfil the echocardiographic criteria for LVNC diagnosis, but only a small proportion (0.9%) of them exhibit other clinical abnormalities suggesting cardiomyopathy [3, 13, 37].

The occurrence of SD seems to be extremely rare in patients with LVNC, if they have no symptoms and in the absence of LV dysfunction [35]. LVNC has not been reported in major epidemiologic studies [6, 7, 35] as the primary cause of death in athletes, and only recently, a very low (1%) incidence of SD/CA related to LVNC has been recently reported among US competitive athletes [8].

Risk stratification is necessary with a complete evaluation, including CMR, exercise echocardiography, and ambulatory ECG monitoring to assess the presence of LV dysfunction, LV fibrosis, cardiac thrombi, or occurrence of arrhythmias during exercise [3, 13, 35, 37, 38].

According to the recent European guidelines [3, 13], individuals with unequivocal/reasonable diagnosis of LVNC may be considered at “low risk” if they have no symptoms, normal LV function, no occurrence of frequent and/or complex ventricular arrhythmias on ambulatory ECG monitoring and exercise ECG testing, and no prior history of unexplained syncope [3, 13]. Regular follow-up is recommended for individuals with LVNC and new symptoms should prompt re-evaluation [13].

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Arrhythmogenic Cardiomyopathy

5

Cristina Basso, Monica De Gaspari, Stefania Rizzo, and Gaetano Thiene

5.1 Introduction

Arrhythmogenic cardiomyopathy (AC) has been described as a major cause of sudden death (SD) in the young and athletes in the 1980s, based upon the early data of a series of the SD Registry, Veneto region, Northeast Italy [1, 2]. The discovery was not easily accepted by the scientific community, since at that time only hypertrophic cardiomyopathy (HCM) was reported as a cardiomyopathy at risk of life-threatening arrhythmias during effort [3]. Moreover, AC was not yet recognized as a cardiomyopathy by the WHO [4], becoming part of this group of cardiac diseases only in the revised 1995 WHO classification [5].

The distrust in recognizing AC as another disease at risk of SD in the young and athlete was justified not only by the need to accept a new nosologic entity but also by the fact that while HCM was affecting the left ventricle, i.e. the ventricle of cardiac output, AC was initially described as a disease of the right ventricle, with mild or even absent left ventricular involvement. It was indeed difficult to understand why young people with a right ventricular disease and a normal left ventricle were at high risk of SD during sport activity.

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5.2 Definition and Pathological Findings

AC is a heredofamilial, genetically determined cardiomyopathy, mostly due to mutation in genes encoding for desmosomal proteins [6–8]. An age- and gender-related penetrance of the AC phenotype is well described, and SD typically occurs during adolescence or early adulthood, even as the first manifestation of the disease [9].

The acquired, although genetically determined, atrophy of the ventricular myocardium is substituted by fibro-fatty tissue, as a repair consequence of a progressive cardiomyocyte death, either necrosis or apoptosis [10]. The process starts from the subepicardium and deepens as a wave-front phenomenon, to reach the subendocardium, eventually becoming transmural. The transmural involvement is the prerequisite for the development of aneurysm, typically located in the so-called triangle of dysplasia, i.e. the inflow, apex and outflow of the right ventricle. In advanced forms, the free wall can appear very thin, parchment-like due to the almost total disappearance of the myocardium and ventricular cavity can enlarge. The extent of the disease can be either segmental (Fig. 5.1) or diffuse (Fig. 5.2), and wall thinning and aneurysms are not necessary to reach the diagnosis, so that only histology may reveal the disease (Fig. 5.3) [11]. Cases with early stages of myocardial injury preceding the mature stage of fibro-fatty tissue replacement have been reported. While the original description was pointing to a constant right ventricular involvement, genotype-phenotype studies, together with pathological and cardiac magnetic resonance investigation, demonstrated that biventricular or even isolated

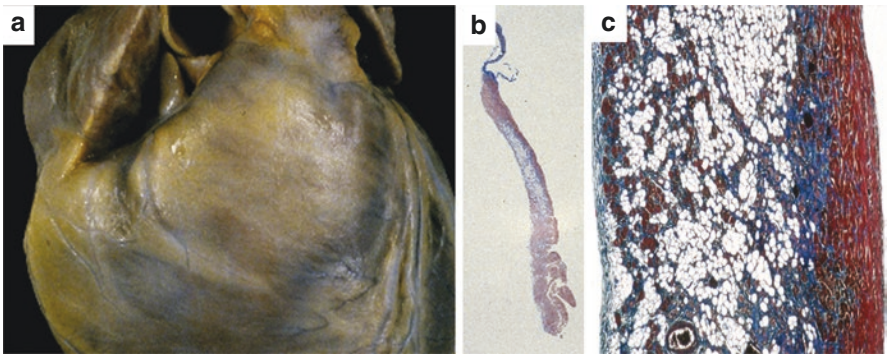

Fig. 5.1 AC segmental form, a 26-year-old male athlete, SD on effort. (**a**) Dilated right ventricular outflow tract. (**b**) Panoramic histologic section of the right ventricular outflow tract wall showing segmental fibro-fatty replacement (Heidenhain trichrome stain). (**c**) Close up of (**b**) showing the residual cardiac myocytes entrapped within fibrous and fatty tissue (Heidenhain trichrome stain)

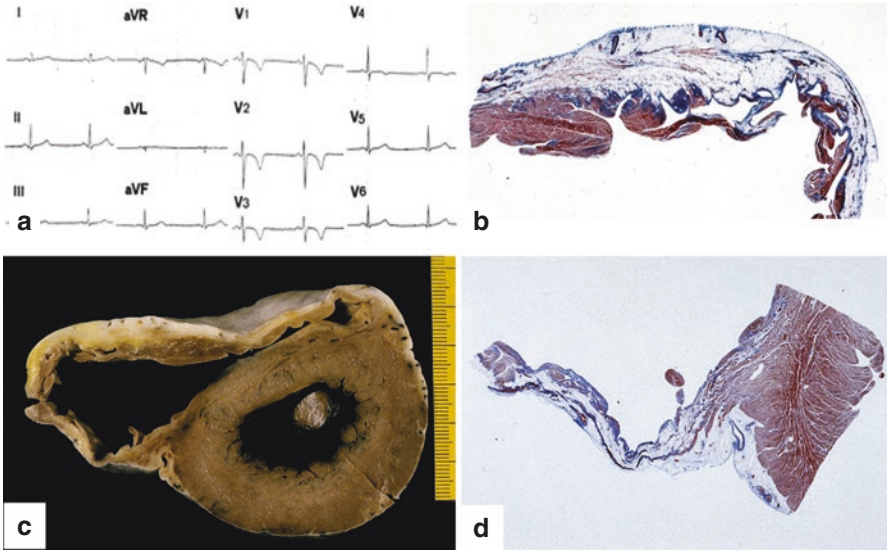

Fig. 5.2 AC diffuse form, a 17-year-old male athlete, SD on effort. (**a**) Basal 12 lead ECG showing inverted T wave in right precordial leads up to V4. (**b**) Mid-ventricular cross section of the heart, with aneurysms in the anterior and posterior right ventricular free walls. (**c**) Panoramic histologic section of the anterior right ventricular free wall showing transmural fibro-fatty replacement (Heidenhain trichrome stain). (**d**) Panoramic histologic section of the posterior right ventricular free wall showing thinning with aneurysm due to transmural fibro-fatty replacement (Heidenhain trichrome stain)

or dominant left ventricular forms do exist (Fig. 5.4) [7, 10, 12–16]. This has led to the new designation of AC that represents the evolution of the original acronym "ARVC", reflecting the evolved concept of a biventricular myocardial disease where the left ventricular involvement may parallel or even exceed the right ventricular involvement.

Noteworthy, left ventricular free wall involvement was already reported in up to 70% of autopsy reports of classical right ventricular variants [10, 12], and in this setting, the subepicardium and mid-myocardium of the posterolateral wall is typically affected.

When the biventricular involvement is diffuse, AC may mimic dilated cardiomyopathy and can even require cardiac transplantation. The ventricular septum involvement remains exceptional, being reported in about 20% of cases, usually on the right side.

Isolated fatty tissue at postmortem cannot be regarded as a variant of AC, and this is of utmost importance since a misdiagnosis of AC can carry forensic and preventive implications [17].

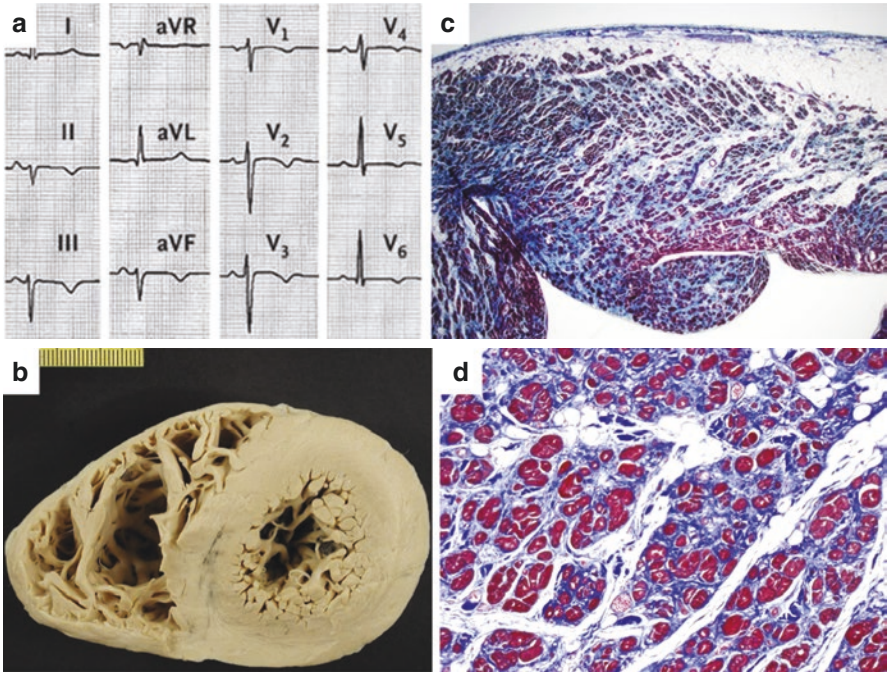

Fig. 5.3 AC diffuse form, a 24-year-old male athlete, SD on effort. (**a**) Basal 12 lead ECG showing diffuse T wave inversion. (**b**) Mid-ventricular cross section of the heart with a dilated right ventricular chamber, hypertrophied subendocardial trabeculae, in the absence of aneurysm formation. (**c**) Transmural histologic section of the anterior right ventricular free wall showing fibro-fatty replacement (Heidenhain trichrome stain). (**d**) Close up of (**b**) showing the residual cardiac myocytes entrapped within fibrous and fatty tissue (Heidenhain trichrome stain)

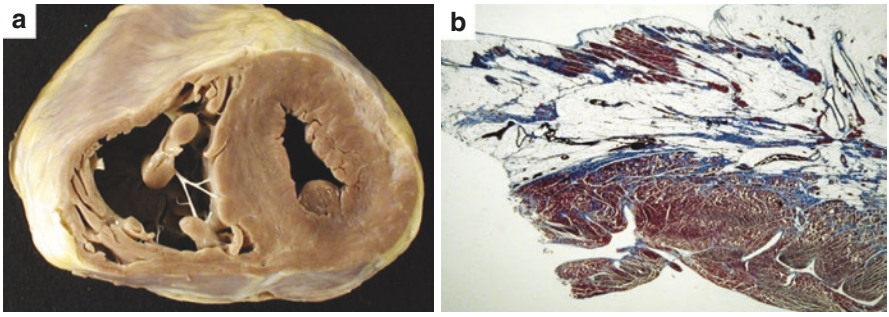

Fig. 5.4 AC left ventricular variant, a 36-year-old male, SD on effort. (**a**) Mid-ventricular cross section of the heart with normal appearance of right ventricular and septal myocardium but the whitish subepicardial appearance of the lateral left ventricular free wall. (**b**) Panoramic histologic section of the lateral left ventricular free wall showing subepicardial fibro-fatty replacement (Heidenhain trichrome stain)

5.3 Pathophysiology of Ventricular Arrhythmias in AC

To explain the arrhythmogenicity of AC, several structural and functional factors have been advanced [18, 19]. The fibro-fatty replacement of the myocardium accounts for the QRS widening and post-excitation epsilon; similarly to ischemic scars, the fibro-fatty scar hinders the intraventricular electrical impulse transmission, facilitating re-entry phenomena. Right ventricular aneurysms and chamber dilatation further slow down the intraventricular conduction and favour re-entry mechanisms. "Poussées" of AC progression, with cardiomyocyte necrosis and inflammatory infiltrates, may trigger life-threatening arrhythmias [20, 21]. The occurrence of electrical instability also in the pre-phenotypic stage of AC is still debated [7, 22]. A crosstalk between mechanical junction and ion channels could lead to lower sodium current density, slow conduction and increased arrhythmia susceptibility. However, so far no SD case has been reported occurring in the pre-phenotypic stage of AC with documented histopathology and genetic findings to support this hypothesis.

5.4 AC and SD in Athletes

We demonstrated that among cardiovascular diseases at risk of SD in athletes, AC (Fig. 5.5) and coronary artery disease, either congenital or atherosclerotic, are associated with the greatest risk [23, 24].

Our data were different from existing US studies showing a higher prevalence of other cardiovascular diseases such as HCM, anomalous coronary arteries and myocarditis [25].

Italian data are obviously influenced by the obligatory screening of competitive athletes, which has been in practice in Italy since the 1980s. In fact, pre-participation

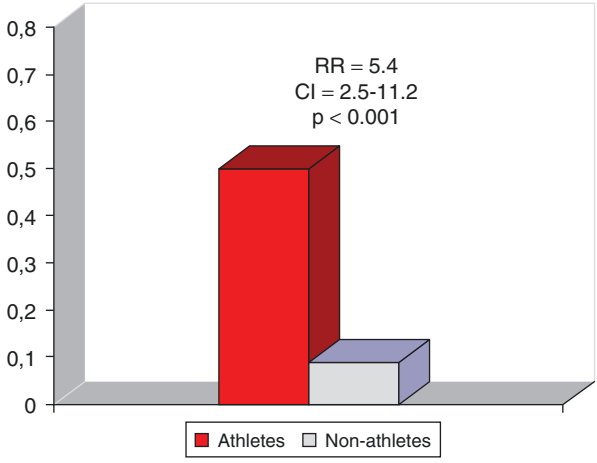

Fig. 5.5 Incidence and relative risk (RR) of SD for AC. A fivefold increase of SD among athletes vs non-athletes is evident (modified from Corrado et al., [24])

screening including 12 lead ECG has successfully prevented SD from HCM, through the early identification and consequent disqualification from sport activity of affected athletes [26]. On the contrary, coronary artery disease which is rarely suspected on the basis of 12 lead ECG or limited stress test was missed at the screening so that the prevalence was not modified. Prevalence of AC in major published series of SD in the young and athletes is reported in Table 5.1 [15, 24, 25, 27–33].

To explain the high incidence of AC as a cause of SD during sport activity in Italy, many factors have been claimed.

The early theory of the high prevalence of AC due to genetic factors in this geographic area has been soon abandoned. A difference from other studies was data collected by coroner or media reports; in the Veneto Region SD registry, a morphologic examination of all hearts was performed by the same team of experienced cardiovascular pathologists according to a standard protocol [34]. The disease in the early stages present subtle changes, and only a careful gross and histologic examination can detect the substrates allowing the final diagnosis. On the other hand, the high prevalence of AC in SD series in Italy, despite the obligatory pre-participation screening including 12 lead ECG, finds various explanations. Standardized diagnostic criteria for AC became available only in 1994 [35], and they needed some years to be rigorously applied by sport physicians. These criteria were then modified only in 2010 [36]. Meanwhile, left dominant AC forms were recognized, and they still escape classical ECG diagnostic criteria so that asymptomatic athletes are not identified [14, 16].

Table 5.1 AC as a cause of sudden death in the young and/or athletes (autopsy-proven)

Study	Country	*N*, age (years)	AC %
Burke et al. (1991)	USA	34, 14–40 Athletes	3
		656, 14–40 Non-athletes	0
Wisten et al. (2002)	Sweden	181, 15–35	6.6
Corrado et al. (2003)	Italy	55, 12–35 Athletes	21.8
		245, 12–35 Non-athletes	10.2
Di Gioia et al. (2006)	Italy	100, 1–40	12
Margey et al. (2011)	Ireland	116, 15–35	1.7
Eckart et al. (2011)	USA	298, <35	1.3
Winkel et al. (2011)	Denmark	314, 1–35	5
Finocchiaro et al. (2016)	United Kingdom	258, 7–35 (<18 years = 79, 18–35 years = 179) Athletes	6 14
Bagnall et al. (2016)	Australia and New Zealand	490, 1–35	NA[a]
Maron et al. (2016)	USA	842, 14–23 Athletes	5

[a]6% all cardiomyopathies, including dilated, hypertrophic and arrhythmogenic

Competitive sport activity causes a fivefold increase in the risk of SD in adolescents and young adults affected by AC [24].

The frequent occurrence of SD during effort can be explained by mechanical stretch, due to increased ventricular preload during effort. Both experimentally and clinically, it has been demonstrated that physical exercise favours AC progression and worsening of the arrhythmic substrate due to increased mechanical wall stress and adrenergic stimulation [37–40]. Endurance sports and strenuous physical exercise increase age-related penetrance and occurrence of ventricular arrhythmias and heart failure in AC desmosomal gene mutations carriers. For this reason, the scientific evidence supports the concept that in AC patients participation in high-intensity sports should be discouraged, because it is associated with accelerated disease progression, greater risk of ventricular arrhythmias and major events [41, 42]. This is also applicable to so-called "healthy" genetic carriers, in the absence of overt disease phenotype.

5.5 Early Identification at Pre-participation Screening

We clearly demonstrated that physical exercise was not the cause of enhanced mortality, but it triggered SD in those athletes who were affected by cardiovascular conditions predisposing to ventricular arrhythmias during physical exercise, such as AC and congenital coronary artery anomalies [24]. Every effort should be made to identify these diseases in athletes, because the simple disqualification of affected athletes is life-saving.

Besides symptoms such as syncope, palpitations or chest pain, athletes are referred to exclude the presence of AC due to ECG changes, such as depolarization abnormalities, QRS widening, epsilon waves, and repolarization changes with inverted T waves on precordial leads, and ventricular arrhythmias with a left bundle branch block morphology [6, 43].

Since there is no single gold standard, AC diagnosis requires multiple criteria, combining morpho-functional assessment (echocardiography, cardiac magnetic resonance - CMR, and exceptionally angiography), tissue characterization, ECG, arrhythmias and familial history [36]. Diagnostic criteria were revised in 2010 including quantitative data and genetics, to improve diagnostic sensitivity, by maintaining diagnostic specificity. However, caution is recommended since the pathogenic significance of a single mutation is increasingly questioned, particularly in the era of next-generation sequencing).

Although direct tissue characterization is obtained only through endomyocardial biopsy (EMB) [44], the increasing availability of "not direct" techniques, such as contrast-enhanced CMR (CE-CMR) and electro-anatomic mapping [45–48], limits the EMB indication to selected cases of proband reaching the possible or probable diagnosis, to upgrade the score, and to non-familial AC for differential diagnosis with phenocopies. Specifically, EMB is indicated in probands with a sporadic form of ACM and negative genotyping, in whom the ultimate diagnosis depends on the

histologic study of the myocardium to exclude mimics such as myocarditis, sarcoidosis or other heart muscle disorders.

In the last decade, the exploding use of CE-CMR in the routine workup increasingly revealed left dominant variants of AC which escape clinical identification. They are often not recognized at the pre-participation screening so that they can cause SD in competitive athletes, in the absence of proper cardiovascular emergency care on the field [49]. ECG abnormalities such as lateral or inferolateral T-wave inversion, low-voltage QRS complex on peripheral leads and right bundle branch block/polymorphic ventricular arrhythmias suggest a left-side involvement. The Padua criteria have been recently proposed to fill the gap of 2010 criteria, with the introduction of new diagnostic criteria regarding CE-CMR tissue characterization, depolarization/repolarization ECG abnormalities and ventricular arrhythmia features for diagnosis of the left ventricular phenotype [50].

Finally, the differential diagnosis between athlete's heart and AC may be challenging. A comprehensive echocardiographic assessment of right ventricular morphology and function could provide relevant information and properly guide the indication to CMR. While intense physical training may be associated with reversible dilatation of both ventricles, with preserved systolic function, both global and regional, and a normal (<0.9) right/left ventricle ratio, AC diagnosis requires the combination of right ventricular dilatation or dysfunction and regional wall motion abnormalities. CMR may provide additional information because of its ability to demonstrate the presence of fibro-fatty replacement [51]. However, the integration of cardiac imaging findings with 12 lead ECG signs, clinical signs and symptoms, family history, and arrhythmias is crucial to achieving the final diagnosis.

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Acute and Chronic Myocarditis

6

Pietro Delise, Monica Centa, Gianluca Piccoli, and Marco Scorcu

Acute myocarditis, an inflammatory disease of the myocardium, has various causes, the most common being viral infection [1] (Table 6.1).

In acute myocarditis of viral origin, viruses enter the cardiomyocytes, causing cytopathic effects due to viral replication. This triggers a humoral and cellular response that includes immune reactions [1].

Acute myocarditis is characterized by edema and infiltration of pan T lymphocytes and macrophages; variable amounts of myocardial necrosis may occur [1–4].

While the precise incidence of acute myocarditis is unknown [1, 5–7], it is probably higher than generally thought. Indeed, myocarditis is often a collateral effect of influenza syndromes, and if it does not cause major symptoms, it is not diagnosed at all.

Acute myocarditis is one of the causes of sudden death in athletes, as demonstrated by Italian and USA research [8, 9] (Fig. 6.1). Some experimental studies in animals [10–12] suggest that physical activity during acute myocarditis increases the replication and aggressiveness of the virus. It follows that, in order to prevent sudden death, early identification of acute myocarditis in athletes is essential, so that the individual can rest and avoid exercise. In real life, however, during febrile

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Table 6.1 Causes of myocarditis (From Caforio A et al. 2013, modified)

Infectious	
Viral	RNA viruses: Coxsackieviruses A and B, echoviruses, polioviruses, influenza A and B viruses, etc.
	DNA viruses: adenoviruses, parvovirus B19, cytomegalovirus, human herpes virus-6, etc.
Rickettsial	*Coxiella burnetii* (Q fever), etc.
Spirochetal	*Borrelia* (Lyme disease), *Leptospira* (Weil's disease)
Bacterial	*Staphylococcus*, *Streptococcus*, *Pneumococcus*, etc.
Fungal	*Aspergillus*, etc.
Protozoal	*Trypanosoma cruzi*, *Toxoplasma gondii*, etc.
Parasitic	*Trichinella spiralis*, etc.
Immune-mediated	
Autoantigens	Infection-negative lymphocytic, infection-negative giant cell associated with autoimmune or immune-oriented disorders: systemic lupus erythematosus, rheumatoid arthritis, Churg-Strauss syndrome, etc.
Allergens	Tetanus toxoid, vaccines, serum sickness Drugs: penicillin, colchicine, etc.
Alloantigens	Heart transplant rejection
Toxic	
Drugs	Amphetamines, cocaine, ethanol, etc.
Hormones	Pheochromocytoma, etc.
Etc.	
Other	

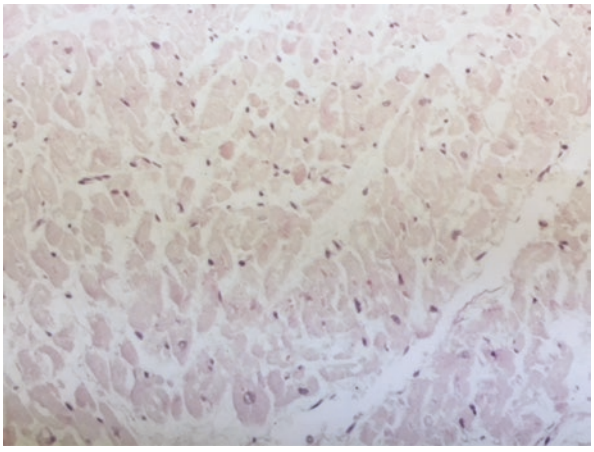

Fig. 6.1 Male, 25 years old, soccer player who suddenly died during physical training. The autopsy revealed an acute myocarditis. Istologic finding is reported which shows a diffuse infiltration of lymphocytes

syndromes, athletes frequently treat their symptoms aggressively with anti-inflammatory drugs and resume physical training as soon as possible.

Sudden death during myocarditis can occur both at rest and during effort and is determined by rapid and often polymorphic ventricular tachycardia, which may degenerate into ventricular fibrillation (Figs. 6.2 and 6.3).

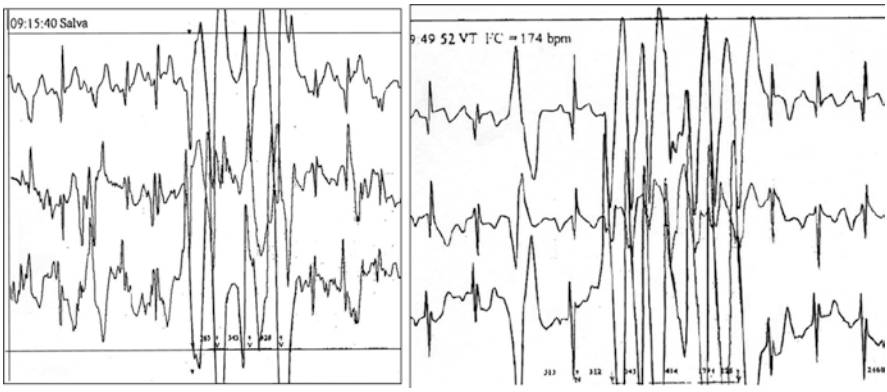

Fig. 6.2 Male, 21 years old. Syncope during soccer. Holter monitoring showed fast, polymorphic non-sustained ventricular tachycardia. A few days later, he suddenly died during a football match. Autopsy revealed acute myocarditis

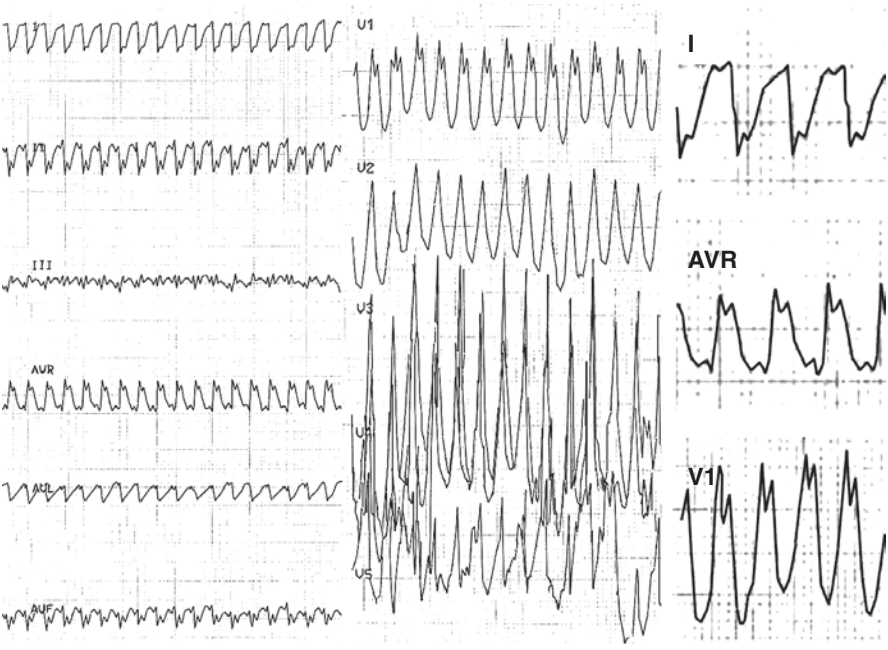

Fig. 6.3 Male, 14 years old. During a febrile episode, he experienced palpitations and pre-syncope. The ECG performed in the hospital showed fast ventricular tachycardia (VT). Note the morphology of QRS: RBBB with superior axis oriented towards aVR. This morphology indicates that VT arose from the infero-lateral part of the left ventricle

6.1 Clinical and Electrocardiographic Findings

The disease generally begins with fever and may present in many different ways, ranging from mild symptoms to chest pain, palpitations, etc. [1]. Only a few patients present with left ventricular dysfunction; in these cases, the disease can cause heart failure. In some cases, syncope and/or cardiac arrest may occur as a consequence of cardiac arrhythmias (see above).

The diagnosis of myocarditis is generally reached on the basis of a clinical suspicion and alterations of the electrocardiogram (ECG) [13–20].

In the acute phase, the ECG frequently shows ST elevation in infero-lateral leads (Fig. 6.4a). Of note, the presence of ST elevation in the clinical setting of pericarditis is a sign of concomitant myocarditis. Indeed, the pericardium has no electrical activity. ST elevation in myocarditis may resemble transmural myocardial infarction (STEMI). However, the electrophysiological mechanism of ST elevation in the two conditions is different, and some important differences are present. During STEMI, a transmural ischemic injury is determined by thrombotic occlusion of a coronary artery. Consequently, major modifications of monophasic action potential (MAP) occur in this area, i.e., reduction in the voltage and duration of MAP, which extends transmurally in the affected area.

Thus, in the case of STEMI, an "ST vector" is generated which is oriented from the normal myocardium (opposite to the ischemic myocardium) to the affected area; this creates ST elevation in leads which explore the ischemic myocardium and ST depression in reciprocal leads [21].

In myocarditis, ST elevation is determined by modifications of MAP that are similar to those seen in STEMI (reduction of voltage and duration) but are localized mainly in intramyocardial and subepicardial layers, while the subendocardium is frequently not involved or less involved.

This phenomenon determines an electrical gradient between the subendocardial and subepicardial myocardium, creating an "ST vector" orientated from the endocardium to the epicardium. This vector is recorded as ST elevation in leads exploring the affected area [22] (Fig. 6.5). In myocarditis, there are no reciprocal leads recording ST depression. The only exception may be an ST depression in aVR, as this lead explores the cavity of the left ventricle and records the negative part of the ST vector (Figs. 6.4a and 6.5).

Despite these differences, the differential diagnosis between myocarditis and STEMI may sometimes be difficult, and coronary angiography may be required.

In addition to ST elevation in the acute phase of myocarditis, QRS modifications may also occur: low and/or fragmented voltages, axis deviation, and also Q waves, which can mimic acute myocardial infarction (Fig. 6.6a, b). All these alterations may be due to edema and/or transient cell injury or may be the consequence of definite necrosis. In the first cases, these alterations are transient (Fig. 6.6a–c), while in the last case they persist chronically. In the subacute phase (i.e., 12–24 h after the acute episode), T-wave inversion occurs in the same leads in which ST elevation was previously recorded (Fig. 6.4b).

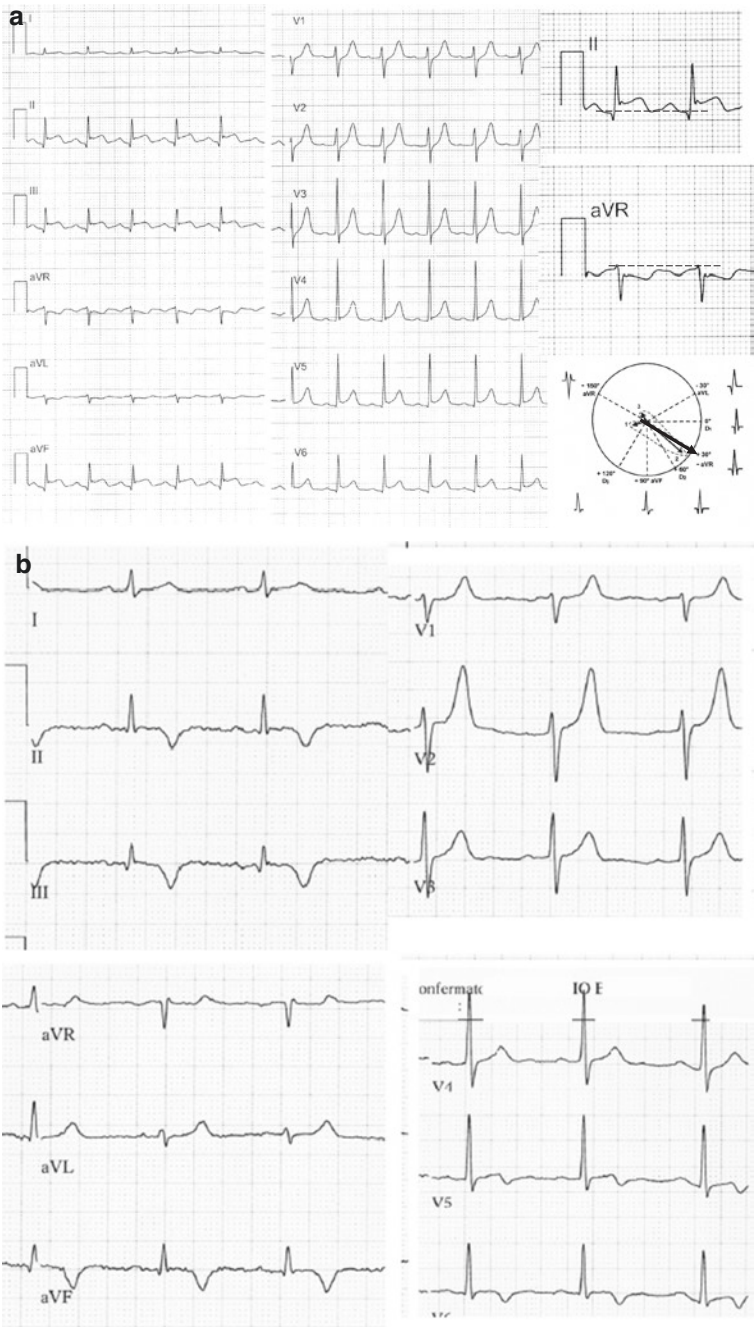

Fig. 6.4 (**a**) Acute myocarditis. The ECG shows ST elevation in infero-lateral leads (II, III, aVF, V5–V6) and ST depression in aVR. (**b**) Same case as in (**a**). ECG recorded after 48 h. Note negative T waves in infero-lateral leads (II, III, aVF, V5–V6). (**c**) Same case as in (**a**, **b**). CMR performed after 48 h. Edema (top) and LE (bottom) can be observed

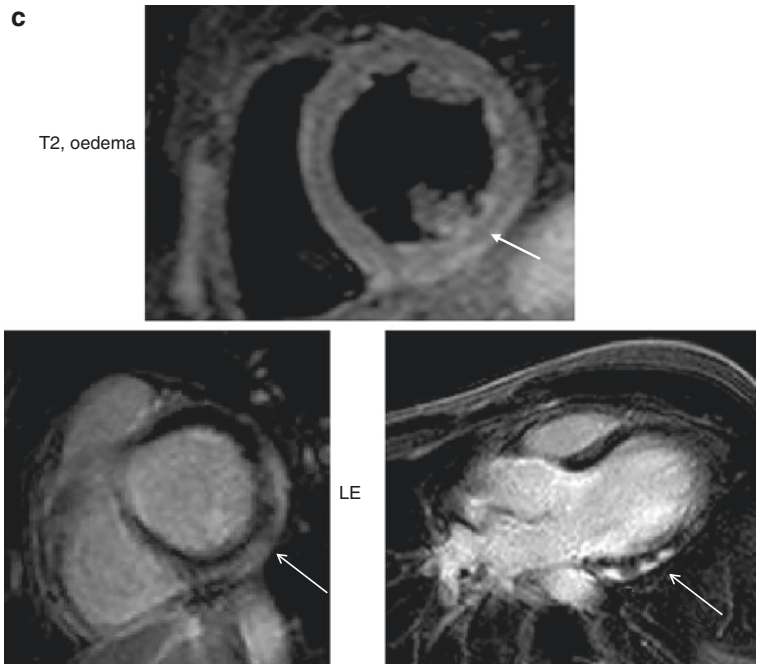

Fig. 6.4 (continued)

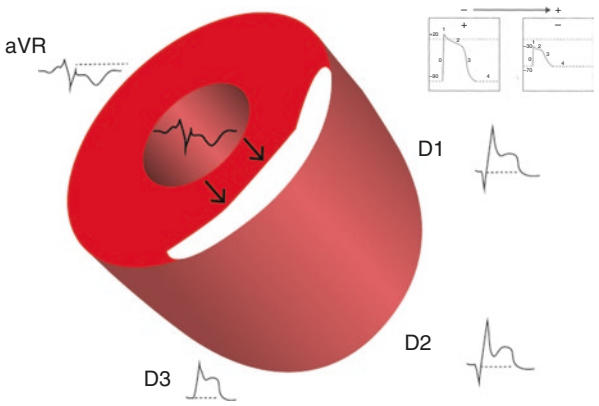

Fig. 6.5 Elecrophysiological mechanism of ST elevation in acute myocarditis. During myocarditis, ST elevation is determined by modifications of monophasic action potential similar to those seen in STEMI (reduction of voltage and duration); these are localized mainly in intramyocardial and subepicardial layers, while the subendocardium is frequently not involved or less involved. This phenomenon determines a gradient between the subendocardial and subepicardial myocardium, creating an "ST vector" orientated from the endocardium to the epicardium. This vector is recorded as ST elevation in leads exploring the affected area. In aVR, ST depression may be recorded, as this lead explores the cavity of the left ventricle and records the negative part of the ST vector

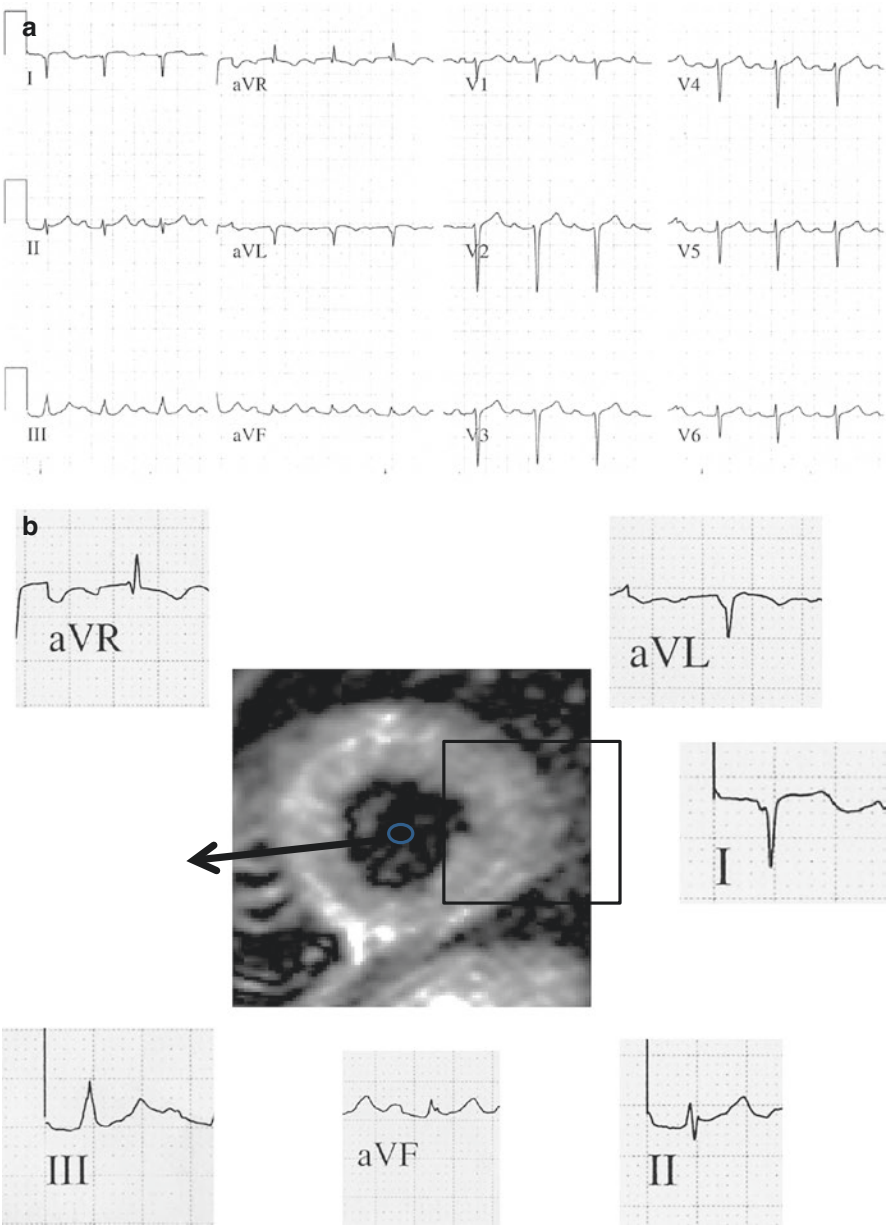

Fig. 6.6 (**a**) Male, 52 years old. Acute myocarditis. The ECG recorded on admission shows ST elevation in I-aVL, right axis deviation, Q waves in I-aVL, and poor R wave progression in precordial leads. (**b**) Same case as in (**a**). CMR performed in the acute phase shows marked edema, particularly in the high lateral wall of the left ventricle. Edema is probably the cause of Q waves in leads (I, aVL) exploring this area. (**c**) Same case as in (**a**, **b**). The ECG performed 6 months later shows normalization of the ECG and, in particular, the disappearance of Q waves in I-aVL

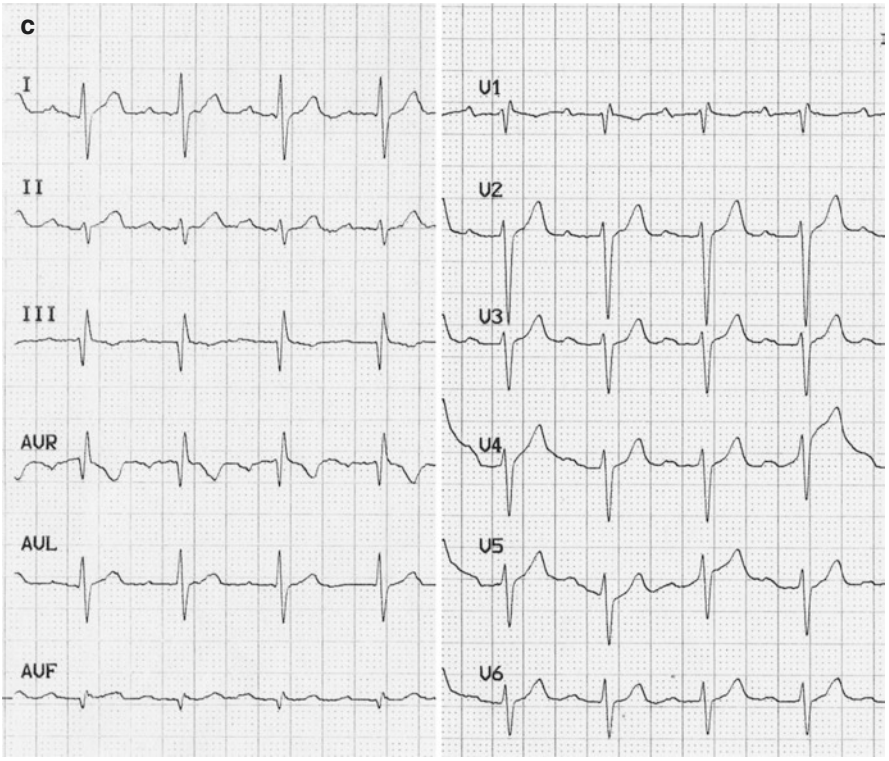

Fig. 6.6 (continued)

The electrophysiological mechanism of T-wave inversion does not have an experimental basis. Nevertheless, T-wave inversion is correlated with the persistence of edema and is probably determined by prolongation of action potential duration.

In patients with Lyme disease or giant cell myocarditis, AV block can develop.

In myocarditis, myocardial damage is documented by the increase of serum enzymes (CK, CKMB, troponins).

Not all patients with myocarditis are medically examined in the acute phase. Some are examined only days or weeks later. In these cases, the suspicion of myocarditis should be aroused in the presence of a clinical history of fever and chest pain and of the new appearance of negative T waves in the ECG.

6.2 Additional Instrumental Findings (Imaging Techniques and Endomyocardial Biopsy)

In many cases of myocarditis, particularly in mild forms, the echocardiogram does not yield useful information. In other cases, depending on the degree of inflammation, regional wall motion abnormalities and systolic dysfunction with preserved

ejection fraction may be present. In rare fulminant myocarditis, the echocardiogram reveals a non-dilated, thickened and hypocontractile left ventricle, as the intense inflammatory response results in massive interstitial edema and loss of contractility [1].

Recently, cardiovascular magnetic resonance (CMR) imaging has been introduced into clinical practice; this provides noninvasive tissue characterization of the myocardium and can efficaciously support the diagnosis of myocarditis. Indeed, in addition to evaluating volumes and contractility, CMR is able to identify both edema and tissue damage. Edema is identified by T2-weight images; myocardial damage is recognized by means of gadolinium late enhancement (LE) (Fig. 6.4c).

Edema is generally present in subepicardial layers and causes an increase in myocardial thickness. CMR visualizes edema as white images within the dark normal myocardium (Figs. 6.4c and 6.6c). Gadolinium, which is injected intravenously, reaches the myocardial interstitium but does not enter the cells. After a few minutes, however, it disappears from both the vessels and the interstitium.

The persistence of gadolinium LE in the acute phase of myocarditis may be related to pathological membrane permeability of the cells involved in inflammation or to cellular necrosis. LE appears in CMR images as white areas within dark normal myocardium (Fig. 6.4c).

In the acute phase of myocarditis, LE is found in over 70% of patients [23]. It is localized in the infero-lateral wall in about 35% of cases, in the anteroseptal wall in about 35%, and in other segments in 15%; in the remaining cases, no LE is detected [23]. According to some authors [23], in acute myocarditis, the localization of LE in the anteroseptal wall has a long-term negative prognostic significance.

Endomyocardial biopsy (EMB) is considered the gold standard for the diagnosis of definite myocarditis. EMB shows histological findings typical of myocarditis and helps to identify the etiology and type of the inflammation (e.g., giant cell, eosinophilic myocarditis, sarcoidosis) [1]. In addition, EMB can guide treatment in subjects infection-negative who need immunosuppression. In clinical practice, however, particularly in mild forms of myocarditis, EMB is not necessary for diagnosis, nor does it change the usual treatment; it is therefore not routinely performed. In contrast, EMB is recommended in complicated forms and/or when diagnosis is uncertain.

6.3 Athletes with Fever: What to Suggest to Sports Physicians

As stated above, in an athlete with fever, it is prudent to stop physical activity, training included. If a suspicion of myocarditis arises, an ECG should be performed; assays of cardiac troponins and creatine kinase may be useful, although, when normal, they do not exclude myocarditis (their normality simply indicates the absence of acute necrosis).

When myocarditis is very probable, an echocardiogram and CMR should be performed.

6.4 Long-Term Outcome of Myocarditis: Chronic Persistence of Inflammation and Residual Fibrosis

The evolution of the disease after the acute phase is quite variable, and it may be useful to monitor this by repeating CMR during follow-up. CMR repeated in hospitalized patients 6 months after the acute phase [24] shows complete recovery in about 10% of cases, with the disappearance of both edema and LE. In about 75% of cases, fibrosis can be detected by means of LE persistence. Finally, in about 15% of cases, both edema and LE are present during follow-up, indicating the persistence of inflammation [24].

It is important to remember that the site and distribution of fibrosis due to myocarditis are different from those seen in other diseases. For example, fibrosis of ischemic origin is transmural or subendocardial, while fibrosis due to myocarditis is generally localized in the subepicardial layers and/or is patchy in intramyocardial layers (Fig. 6.7).

6.5 Clinical and Prognostic Significance of Chronically Residual Fibrosis

Clinical experience teaches that, in patients with ventricular arrhythmia and no obvious heart disease, fibrosis is often detected by CMR and may be the consequence of a previous undetected myocarditis.

In these cases, the QRS morphology of ventricular ectopies is generally RBBB-like, with an upward-oriented axis often pointing toward aVR [22]. On the basis of this morphology, it can be deduced that ventricular ectopic beats originate from the infero-lateral wall of the left ventricle. In these cases, CMR detects fibrosis in the same site (Fig. 6.8a–c). Thus, fibrosis is presumably the cause of ventricular arrhythmias.

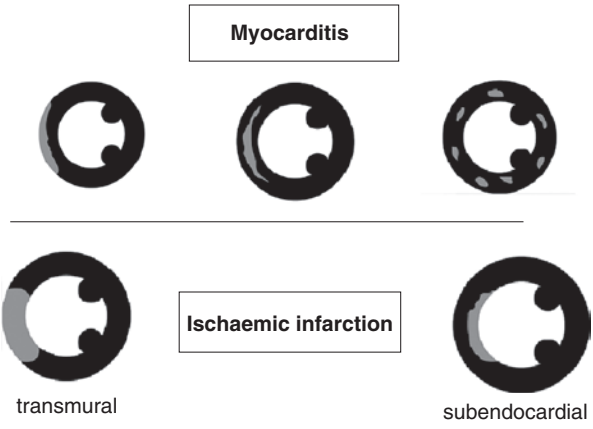

Fig. 6.7 Different localizations of fibrosis (as detected by CMR) in myocarditis and in ischemic heart disease. Top: myocarditis; bottom: ischemic infarction. In myocarditis, LE may be localized at the epicardial level or intramurally. In postinfarction fibrosis of ischemic origin, LE is transmural or localized at the endocardial level

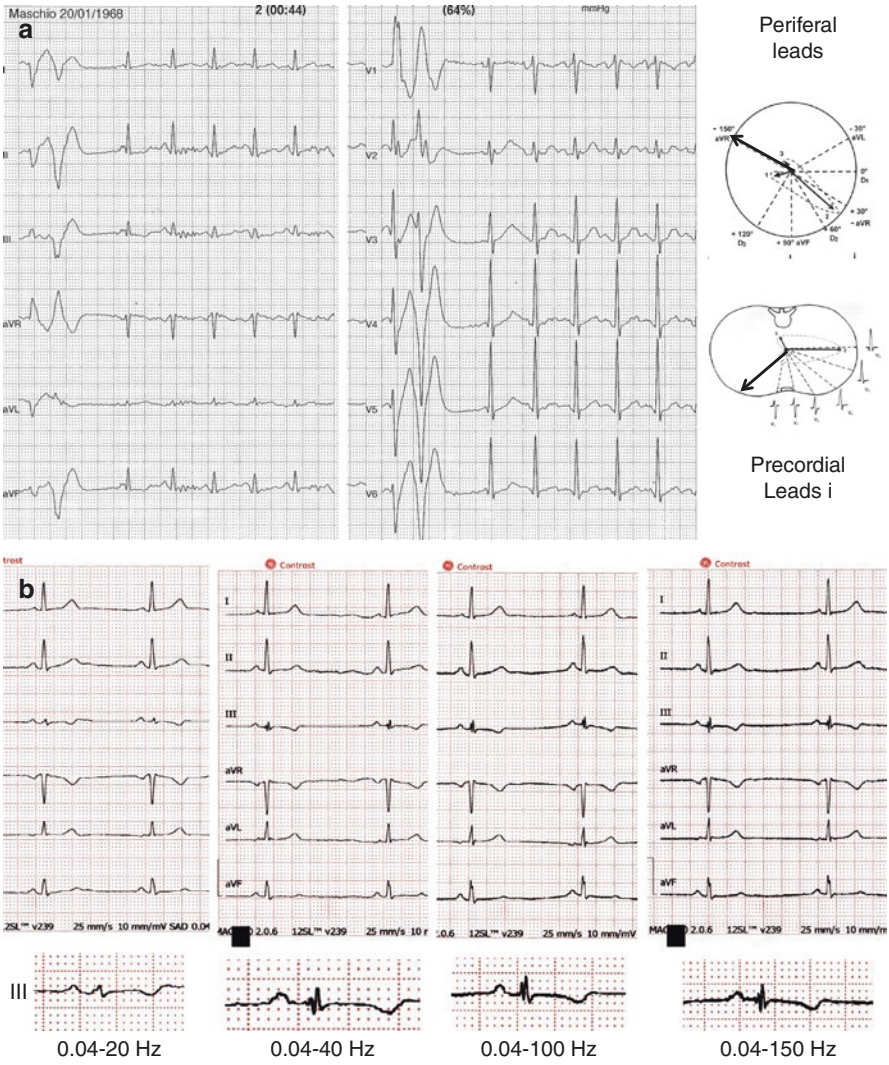

Fig. 6.8 (**a**) Male, 48 years old. ECG during effort shows ventricular premature beats with RBBB-like QRS morphology with upward-oriented axis pointing toward aVR [22]. On the basis of this morphology, it can be deduced that ventricular ectopic beats originate from the infero-lateral wall of the left ventricle. (**b**) Same case as in (**a**). Particular of peripheral leads with different low-pass filters. It can be noted that, when low-pass filters of 0.04–20 Hz are used, no fragmented potentials are recorded. In contrast, fragmented and high-frequency potentials are recorded by using low-pass filters between 0.04–40 Hz and 0.03–150 Hz. (**c**) CMR after gadolinium confirms the presence of fibrosis in the infero-lateral wall of the left ventricle

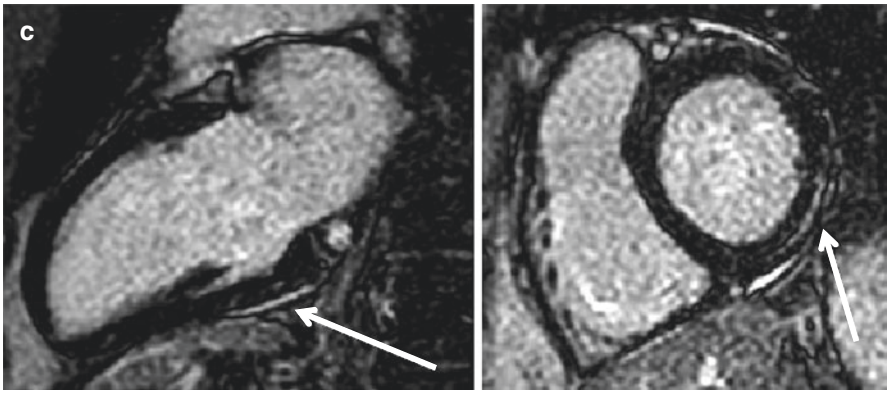

Fig. 6.8 (continued)

Despite these observations, the incidence of ventricular arrhythmias in subjects with post-myocarditis fibrosis is poorly known. Some authors [24] suggest that, during long-term follow-up (7–8 years), patients with residual fibrosis 6 months after the acute phase have a higher incidence of ventricular arrhythmias (VA) than those without fibrosis on CMR.

In such patients, cardiac events (including heart failure and/or malignant VA) have been reported to occur in 11.5% of cases, and in particular, a negative prognostic correlation with the extent of fibrosis has been found. It therefore follows that prudence is recommended in subjects with extensive fibrosis and alarming VA.

In contrast, we do not yet have enough information to establish the risk of patients with limited residual fibrosis and no VA or non-repetitive VA.

6.6 When ECG Suggests the Presence of Fibrosis

Fibrosis of limited extension may produce no ECG signs. Both in myocarditis and in other pathologies (e.g., myocardial infarction) if fibrosis is extensive and diffuse, low voltages, fragmented potentials, and terminal notches can be observed [24–29] (Figs. 6.8b and 6.9a–c). These ECG signs are related to loss of myocardium and delayed activation of peripheral areas, owing to the barriers constituted by fibrotic tissue (Fig. 6.10).

However, it must be stressed that low voltages and fragmented potentials may be recorded if low-pass filters are used in ECG [26]. Indeed, if low-pass filters less than 25–30 Hz (i.e., 0.04–20 Hz) are used, fragmented potentials at high frequency may be eliminated together with artifacts (Fig. 6.8b). In contrast, these potentials may be well recorded by using low-pass filters between 40 and150 Hz (i.e., 0.04–40 or 0.04–150 Hz). In addition, if fibrosis is extensive and compact, Q waves may be recorded in lateral leads or tall R waves in V1, as in ischemic fibrosis. Finally,

fibrosis may produce negative T waves (Fig. 6.11a, b), as a result of late activation of epicardial areas, by inverting the repolarization vector between the endocardial and epicardial myocardium (Fig. 6.12).

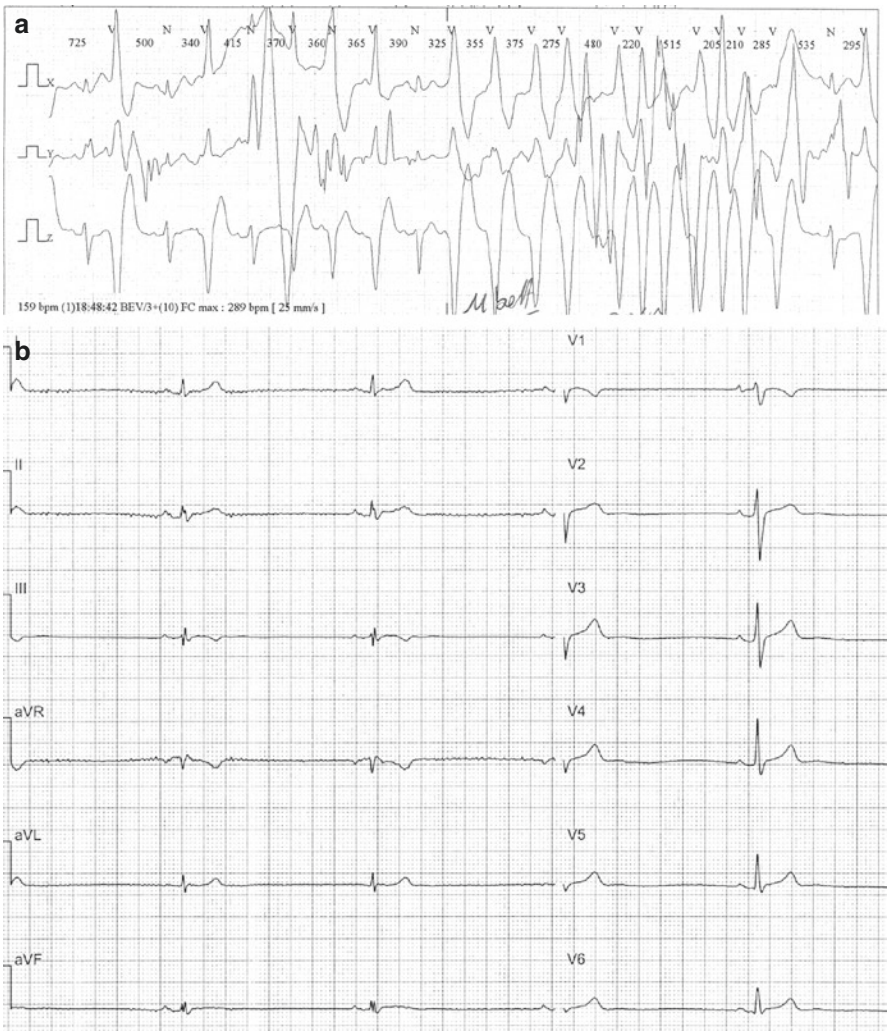

Fig. 6.9 (**a**) Male, 32 years old. Professional soccer player. Holter monitoring performed after a syncope during effort shows polymorphic fast non-sustained ventricular tachycardia (**a**). The basal ECG shows low-voltage QRS in peripheral leads (**b**). (**b**) Same case as in (**a**). During effort testing, fragmented WRS complexes are recorded in II, III, and aVF. (**c**) Same case as in (**a**, **b**). Voltage mapping of the right ventricle (**a**, endocardial) and left ventricle (**b**, epicardial). Diffuse areas of low voltage are documented in both ventricles, which were confirmed by CMR. Biopsy revealed chronic active myocarditis and isolated a virus: HHV6

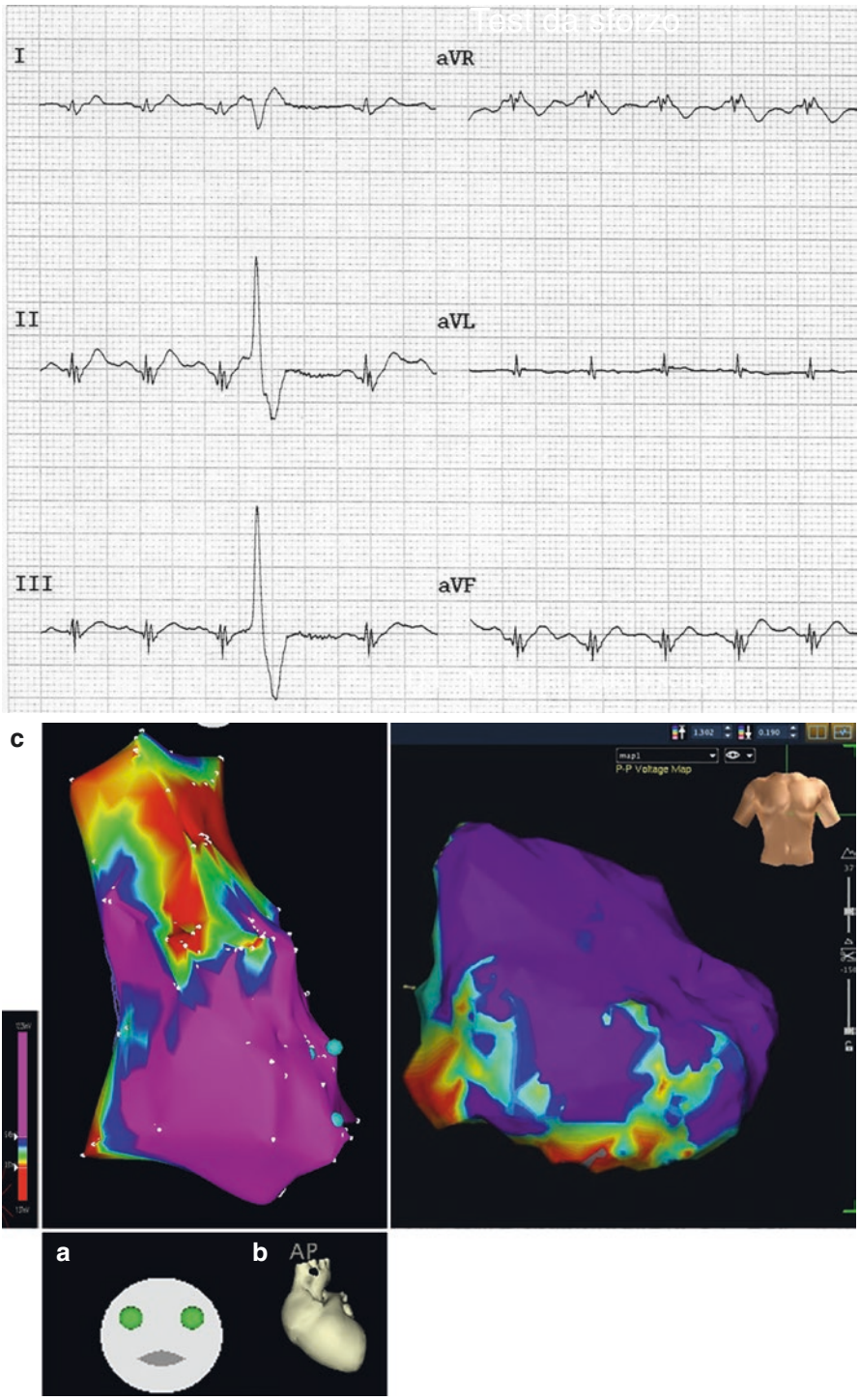

Fig. 6.9 (continued)

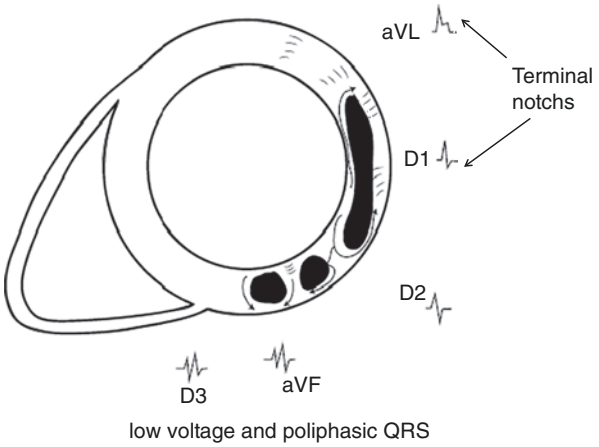

Fig. 6.10 Electrophysiological mechanisms of low-voltage, fragmented potentials, and potentials and notches of QRS complexes determined by fibrosis. For explanations, see text

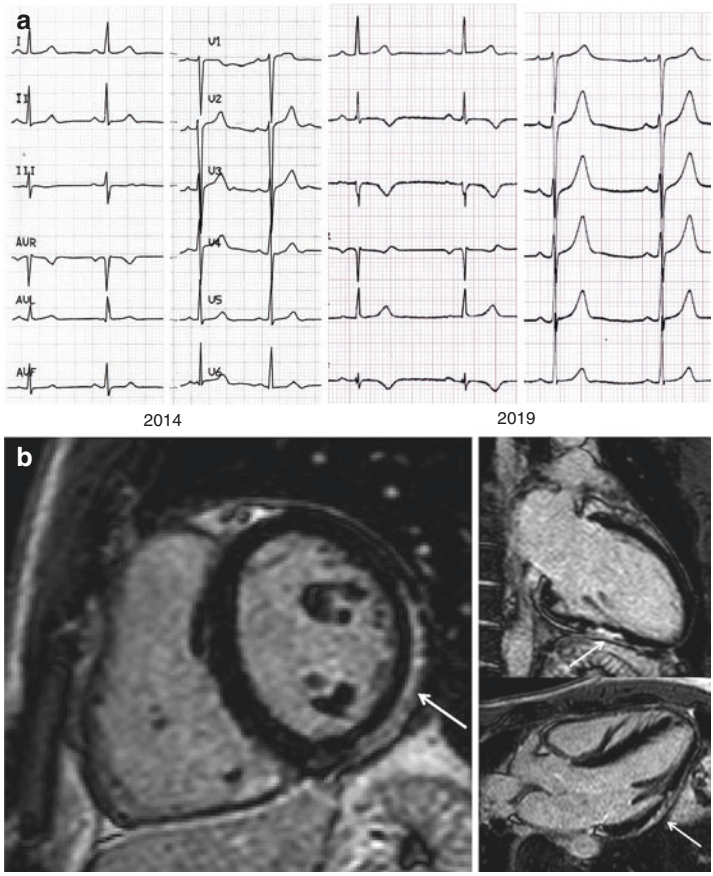

Fig. 6.11 (**a**) Male, 23 years old. He had suffered persistent chest pain 3 months earlier. ECG showed negative T waves in inferior leads, which had been absent 5 years earlier. The ECG aroused the suspicion of previous myocarditis. See also (**b**). (**b**) Same case as in (**a**). CMR confirmed post-myocarditis fibrosis, showing LE in the infero-lateral wall of the left ventricle (arrows)

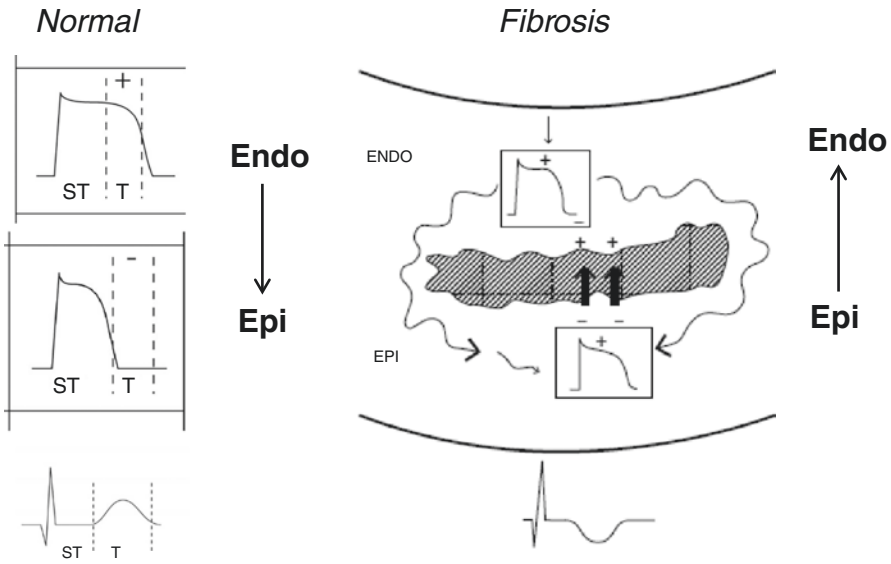

Fig. 6.12 Electrophysiological mechanism of negative T waves in post-myocarditis fibrosis. Fibrosis may produce negative T waves as a consequence of late activation of epicardial areas, inverting the repolarization vector between the endocardial and epicardial myocardium

6.7 Sport Eligibility After Myocarditis

In the absence of fibrosis on CMR and of VA during effort testing and Holter monitoring, eligibility for sport should not be denied. By contrast, it should be denied in the presence of extensive residual fibrosis and significant VA (frequent VPBs, repetitive phenomena). In the case of subjects with limited residual fibrosis and no significant VA, what to do is controversial; eligibility should probably not be denied, as long as strict clinical and instrumental controls are implemented during follow-up.

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Congenital and Acquired Anomalies of Coronary Arteries

7

Paolo Zeppilli, Salvatore Francesco Gervasi, and Vincenzo Palmieri

7.1 Introduction

Congenital and acquired diseases of coronary arteries are frequent causes of sudden cardiac death (SCD) in recreational and competitive sportspeople [1–7]. While coronary atherosclerosis (CA) is responsible for the vast majority of SCD in middle-aged and older athletes (Master) [6, 7], the anomalous origin of a coronary artery from the "wrong" sinus of Valsalva is the second most frequent cause in young athletes in the USA [1] and the third in Italy [2]. Regardless of the type of disease and mechanisms involved, SCD is usually the result of *exercise-induced myocardial ischemia*.

The metabolism of the myocardium is essentially aerobic. The basal oxygen extraction is already high, and an increase in myocardial oxygen consumption (MVO_2) requires a proportional increase in coronary blood flow (CBF). In normal subjects, CBF can increase up to five times during strenuous exercise compared to baseline (*CBF reserve*). MVO_2 is determined by the mechanical work of the heart, heart rate (HR) and wall tension during systole, which in turn depends on the end-diastolic ventricular volume (preload), aortic pressure (afterload) and inotropic state of the myocardium.

The coronary circulation has three functional compartments arranged in series: (1) the epicardial arteries, which have a conductive function and, in physiological conditions, offer minimal resistance to flow; (2) the pre-arterioles, which maintain a constant perfusion pressure at the arteriolar level and offer an appreciable resistance to flow; (3) the arterioles, which are responsible for the metabolic regulation

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of coronary flow, being exposed to substances released locally by the myocardium. They constitute the main component of the resistance of coronary circulation.

When MVO_2 increases, arteriolar resistance decreases in response to local vasodilator metabolites (in particular, adenosine), resulting in an increase in CBF. This, in turn, induces endothelium-dependent vasodilation in the pre-arteriolar and epicardial vessels.

The heart is a particular organ compared to the others, as it generates its own perfusion pressure. During systole, the intramyocardial vessels are subjected to compression which "obstructs" blood flow. Since the pressure is higher at the endocardium than at the epicardium, subendocardial vessels undergo greater systolic compression and need more time to fill and regain their calibre during diastole. This phenomenon is accentuated by tachycardia (which shortens the duration of diastole), by an increase in left ventricular end-diastolic pressure, and by a decrease in coronary perfusion pressure (epicardial coronary stenosis, aortic stenosis, etc.). It is also important to remember that the subendocardial layers have an MVO_2 about 20% higher than the subepicardial ones and consequently a greater susceptibility to ischemia when there is a significant coronary stenosis.

Myocardial ischemia occurs when CBF is inadequate to the metabolic demand [8]. This discrepancy between demand and supply can be caused by increased MVO_2 in the presence of a flow-limiting coronary stenosis, by a primary reduction in flow (functional or mechanical coronary constriction at any level), a thrombosis, or a variable combination of these mechanisms. Ischemia can be *transient* and cause stable or unstable anginal syndromes, or it can be *persistent* and cause cell necrosis and myocardial infarction. Myocardial necrosis depresses contractile function and creates favourable conditions for the occurrence of life-threatening arrhythmias and SCD. In a large infarction, the impairment of the heart's pump function is irreversible and can lead to the development of post-ischemic dilated cardiomyopathy.

7.2 Congenital Anomalies

Congenital coronary artery anomalies (CCAA) are a rare, heterogeneous, group of malformations, isolated or associated with other congenital defects. Their prevalence in the general population (autopsy and retrospective coronary angiography studies) was around 1–2% [9, 10], but in the prospective study of Angelini et al. conducted with precise criteria and a rigorous classification, the prevalence was fairly higher (5.6%) [11]. These differences are partly due to the fact that, from the anatomical point of view, defining what is "normal" or "abnormal" in the coronary tree may be challenging. Generally speaking, we consider "anomalous" a finding that has a prevalence <1% in an unselected general population, even if this criterion is still quite arbitrary.

A few years ago, Yamanaka and Hobbs [9], in a study on 126,595 subjects undergoing coronary angiography, had identified *two main groups of coronary abnormalities*: (1) anomalies of origin and distribution of coronary arteries (87%) and (2) coronary fistulae (13%). On the basis of autopsy data and some pathophysiological

and clinical considerations, the first group was in turn divided into *benign* and *potentially malignant anomalies.*

The CCAA are often discovered incidentally, but the reason why we pay the utmost attention to them is the non-negligible role they can play in the SCD of young sportspeople [1, 2, 12–14]. Subjects with "malignant" CCAA may complain of typical angina, but most of them have *atypical symptoms* like syncope, presyncope, chest discomfort, dyspnoea and palpitations or *may be fully asymptomatic*, being cardiac arrest or SCD the first manifestation of the disease. Furthermore, stress ECG test may show ST-segment depression suggestive of myocardial ischemia, but more often shows non-specific findings (ventricular arrhythmias, T-wave abnormalities, etc.), or is completely negative [13, 14].

Therefore, early diagnosis of CCAA may be very difficult. In the expert hands, transthoracic echocardiography (ECHO) is now considered a reliable non-invasive tool for the initial screening of these anomalies (Fig. 7.1) [14–16], but confirming the diagnosis often requires cardiac magnetic resonance imaging (CMR) or coronary computed tomography angiography (CCTA) [17–19]. The advent of the CCTA has revolutionized the diagnostic approach to these malformations [20, 21]. The continuous improvement in the quality of the image and of the anatomical and functional data that can be obtained today allows an increasingly accurate risk stratification combined with a drastic reduction in the radiation dose [22].

7.3 Anomalous Origin of Coronary Arteries

The "normal" coronary anatomy shows some inter-individual variability. *Normal variants* include (1) left, right or balanced dominance, depending on which coronary artery supply the posterior descending artery; (2) sinoatrial and atrioventricular nodal supply by branches originating from the right (RCA) or the circumflex artery (CX); (3) the "trifurcation" of the left coronary artery (LCA), with a left descending

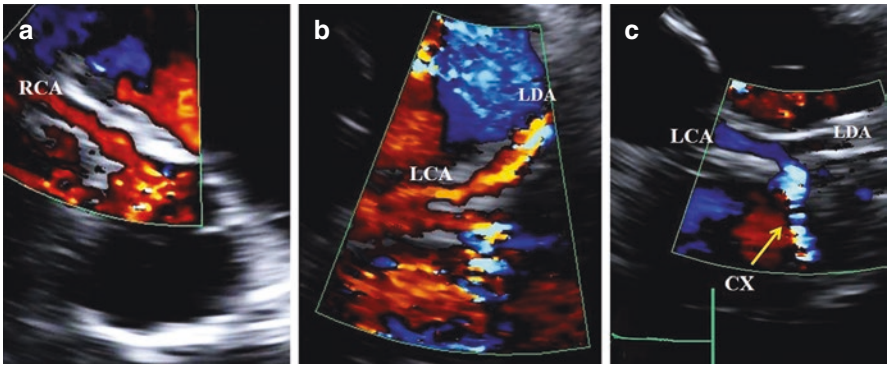

Fig. 7.1 Echocardiographic 2D visualization of (**a**) the right coronary artery (RCA), (**b**) left coronary artery (LCA), (**c**) circumflex artery (CX). Images were obtained by the parasternal short-axis view of the aorta using a low-scale color-Doppler imaging. *LAD* left anterior descending artery

artery (LDA), a CX and a ramus intermedius; (4) the presence of separate ostia of the LDA and CX or of the RCA and conus branch.

Anomalous origins of coronary arteries instead include all the conditions in which one or more coronary branches originate differently from "normal". To this possibility should be added that one or more branches could be hypoplastic (*coronary hypoplasia*) or absent (*coronary aplasia*) [23] or could have an anomalous course along its perfusion territory (*kinking, coiling, myocardial bridge*). The abnormal origin of a coronary artery can occur:

1. *From the pulmonary artery*. In this case, myocardial perfusion is completely dependent on the coronary artery arising from the aorta (AO) which also supplies the anomalous vessel, through which the flow is inverted towards the pulmonary artery (PA), with a left-to-right shunt. The least rare form is the origin of the left main trunk (LMT) from the PA (*Bland-White-Garland syndrome*), a severe malformation, which allows survival until adolescence only in cases (10–20%) in which adequate collateral circulation has developed.

   In the absence of symptoms (angina, syncope, etc.), the diagnosis can be suspected by the finding of a continuous murmur and/or signs of inducible ischemia at the stress ECG test. Transthoracic color-Doppler ECHO, in expert hands, can guide the diagnosis by displaying the abnormal origin of the coronary artery and/or allowing an anomalous continuous flow in the PA to be identified. Transoesophageal ECHO can be useful, but a definitive diagnosis can be obtained, as well as with coronary angiography, with CMR [24], and better with CCTA [25].
2. *From the aorta but from the "wrong" coronary sinus of Valsalva* (RCA from the left sinus and vice versa), with an estimated prevalence in the general population between 0.17% and 0.7% [9–11, 26, 27]. These anomalies can be a "benign" incidental finding but can also lead to severe complications, especially SCD in young athletes [1, 2]. In the study of Corrado [2], the estimated relative risk of SCD in athletes vs non-athletes with such anomalies was 79-fold higher, indicating that *vigorous effort is the main factor in precipitating cardiac arrests*.

   The most common is the anomalous origin of the RCA from the left sinus of Valsalva or from the LCA (AORCA) while the one that seems associated with a greater risk is the origin of the LCA from the right sinus of Valsalva or from the RCA (AOLCA) [14, 28]. From the abnormal ostial position, the coronary artery involved has several potential "paths" that it can travel to get to its perfusion territory:
   (a) *Pre-pulmonic:* anterior to the right ventricular outflow tract (RVOT), usually a benign form with no hemodynamic consequences
   (b) *Retro-aortic:* posterior to the AO between the posterior sinus of Valsalva and the interatrial septum, which usually involves an artery arising from the RCA or from the right sinus of Valsalva;
   (c) *Interarterial:* passing between the AO and PA. This variant has the greatest risk of ischemia and SCD, especially when the first tract of the anomalous vessel passes in close contact (inside) the aortic wall (*intramural/adventitial course*) and/or has other "ugly" anatomical features (see below)

(d) *Trans-septal:* the involved coronary artery has a sub-pulmonic course, passing anteriorly and inferiorly through the interventricular septum, giving off septal branches and then emerging at its normal epicardial position. This anomaly usually involves the LDA or the LMT. Sometimes, it may be difficult to distinguish it from the previous one (interarterial): trans-septal artery does not have a "slit-like" orifice, is surrounded by septal myocardium and shows a downward dip toward a lower position ("hammock sign")

(e) *Retro-cardiac:* the anomalous coronary artery passes behind the mitral and tricuspid valves, in the posterior atrioventricular groove. This is the rarest variant, and its clinical relevance is unclear, but it may be linked to accelerated atherosclerosis due to hemodynamic and endothelial factors

As for the risk of SCD in young athletes, the most malignant variant is undoubtedly the AOLCA, especially if the anomalous artery has a "slit-like" orifice and an interarterial course between AO and PA, and its first tract is intramural/intra-adventitial (Fig. 7.2).

However, cases of SCD or resuscitated cardiac arrests during exercise are reported also in subjects with AORCA [12, 29]. Exercise-induced ischemia depends mostly on the anatomy of the malformation and on different mechanisms that can coexist in the same subject: (1) the acute angle of take-off (<45°) of the anomalous

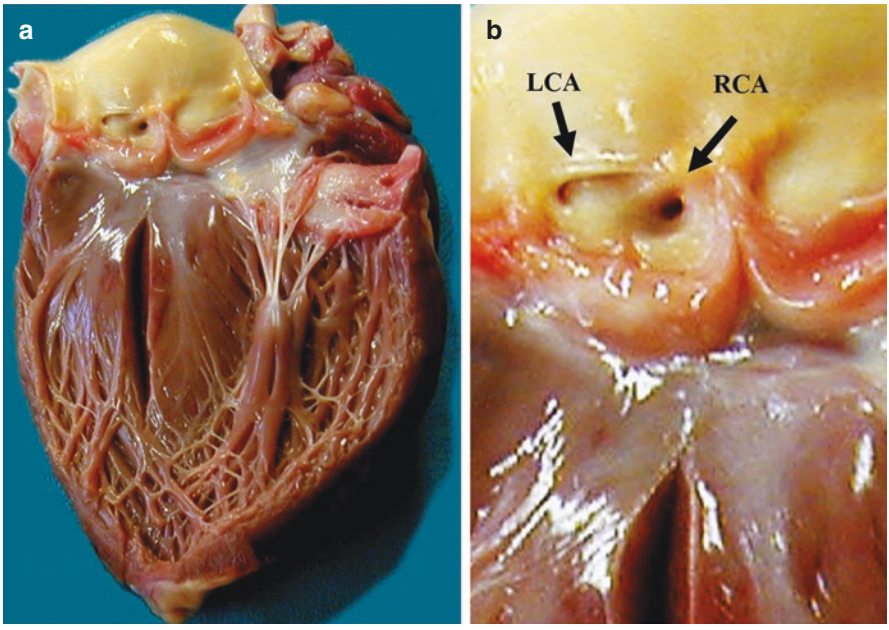

Fig. 7.2 (**a**, **b**) A 12-year-old girl died suddenly after physical education school. Previously, she had no symptoms. (**a**) The autopsy performed at the Institute of Pathological Anatomy of the Gemelli Hospital revealed an anomaly of origin of the left coronary artery (LCA). (**b**) The ostium of the LCA is located next to that of the right coronary artery (RCA) in the right sinus, and it has a "slit-like form"

RCA, with functional closure of *a slit-like orifice*; (2) anomalous RCA compression between the AO and the PA ("sandwich effect") or, more likely, *the obliteration of its lumen with the expansion of the aorta during exercise*; and (3) a first segment hypoplastic and/or intramural/intra-adventitial (Fig. 7.3). Additional factors that could be relevant are the length and calibre of the intramural segment, which can explain why patients with apparently similar anatomy have different clinical profiles and risks [12, 14, 17, 30].

In this context, CCTA is the best imaging technique to define the anatomical details of the anomalous artery and to stratify the risk for optimal management of patients [19]. Some authors proposed precise anatomical CCTA-derived criteria of malignancy such as a minimum lumen area ≤ 4 mm^2, an area stenosis $\geq 50\%$ and an

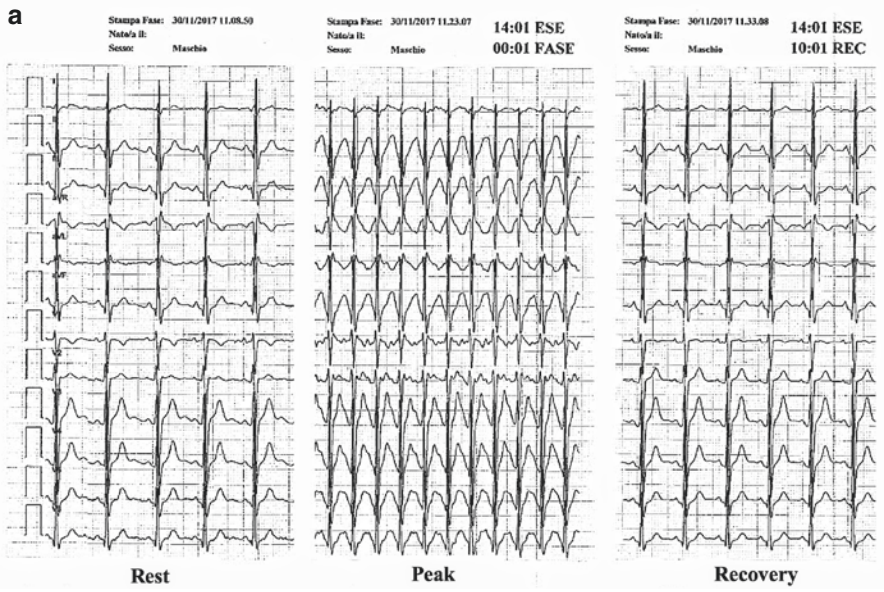

Fig. 7.3 A 14-year-old competitive soccer player. Episodes during matches of "malaise, with paleness, cold sweating and feeling of fainting". Echocardiograms and stress ECGs at two different centres were "negative". The sports physician reassured by the cardiologists issued certification for competitive soccer. However, the boy continues to feel sick when he plays, and the father, worried, asked us for a second opinion. Our rest and stress ECG were completely negative (**a**). Transthoracic ECHO was also negative (**b**, **c**), but an accurate exploration (**d**, **e**) of the aortic root revealed that the right coronary artery (RCA) originated from the left sinus, probably from the left coronary artery (LCA), with an interarterial course between the aorta (AO) and pulmonary artery (PA). Coronary CT angiography (**f**, **g**) confirmed the ECHO diagnosis. In addition, it showed that the first tract of the RCA (broken arrows) was hypoplastic and probably intra-adventitial. A successful surgical unroofing procedure was performed by Prof. Alessandro Frigiola at S. Donato Hospital-Milan, creating a "new" large ostium perpendicular to the aorta (H, solid arrow). After 1 year, the young player returned to competitive soccer without symptoms (with 3 years of follow-up). *Cx* circumflex artery, *LAD* left anterior descending artery

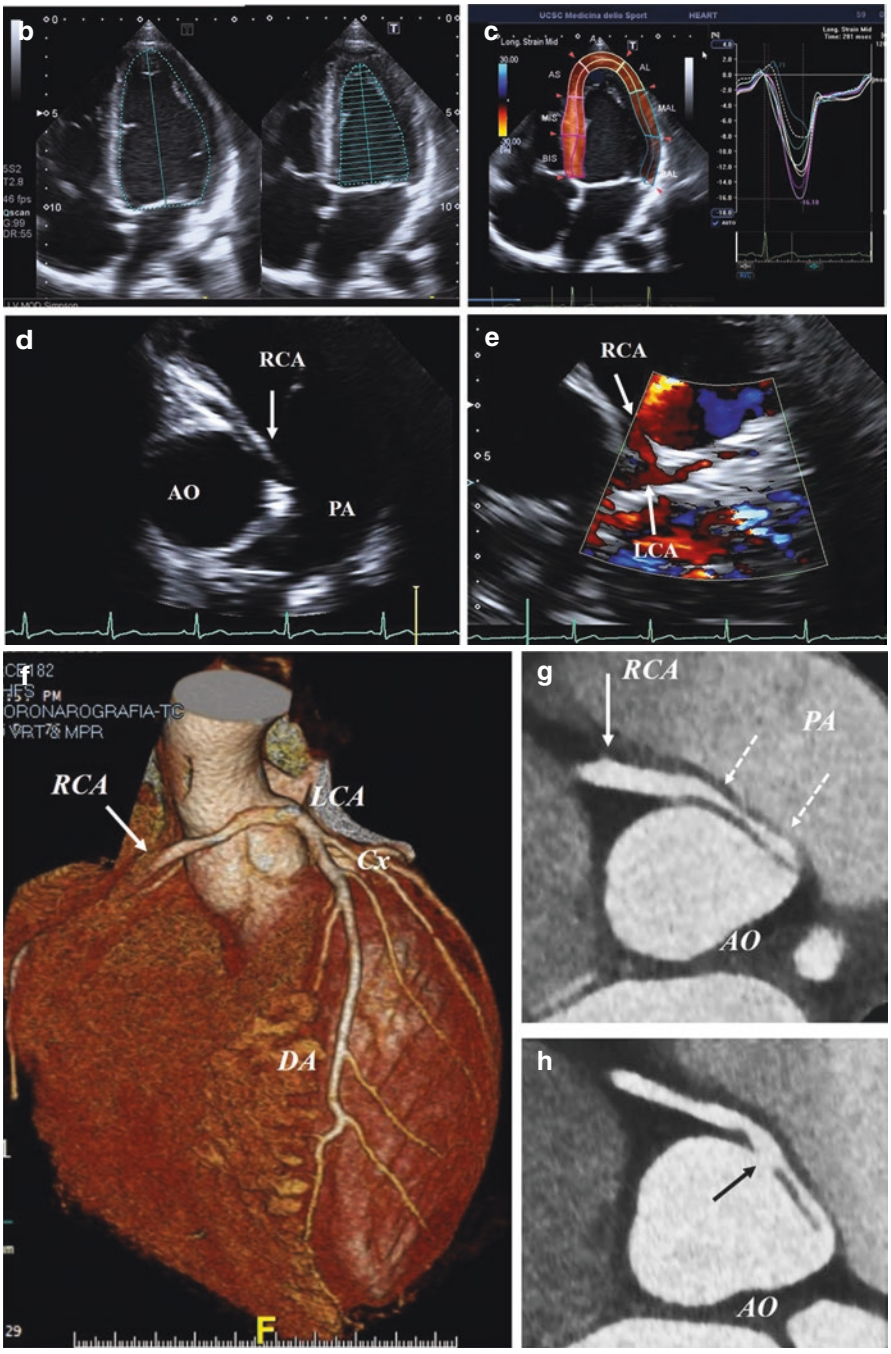

Fig. 7.3 (continued)

intra-arterial tract length >10 mm [31]. For these reasons, the cardio-radiologist should provide an accurate description of all available anatomical features of the anomalous artery, from the morphology of the ostium, the branches it supplies and its distal course.

The ectopic origin of the coronary arteries should not be overlooked. The most important form is the origin above the sino-tubular junction *(high take-off)*. Some of these patients have typical angina or atypical symptoms on exercise, even in the absence of coronary atherosclerotic disease, and in others, the anomaly may evolve in a malignant sense [12, 13]. The high take-off can be associated with an anomalous rotation of the aortic root, which causes the RCA to originate centrally well above the right sinus of Valsalva and follow a short path between the AO and the PA and the LCA above the left sinus of Valsalva with a sharp deviation to the left.

A separate mention should be made for the *anomalous origin of the circumflex artery* (AOCX). The CX, rather than originating from the LMT, arises in a variable angled way from the right sinus and courses along the backside of the AO to its normal position. Three variants were described: in the first, two separate RCA and CX ostia are observed within the right sinus; in the second, the most frequent, there is a common ostium (or two adjacent ostia); in the third, the CX arises from the proximal portion of the RCA [32].

There is still uncertainty about the potential malignancy of this anomaly. Some authors consider it a benign variant [33], although cases complicated by angina and/or myocardial infarction have been described [34, 35]. Many of the subjects with AOCX described in the literature are not athletes, and this generates some difficulty in deciding whether a subject with this anomaly can be considered eligible for competitive sports with high cardiovascular demand, excluding a priori that this anomaly cannot cause a "high-load ischemia". Moreover, in some cases, this anomaly coexists with pathologies such as a hypertrophic cardiomyopathy, coronary atherosclerosis, left bundle branch block (LBBB), symptoms like syncope on exertion or ventricular arrhythmias and signs of inducible ischemia at the stress ECG test. In our opinion, sportsmen with this anomaly must be evaluated carefully and in a global way, placing the anomaly in the context of the age, clinical history, eventually concomitant pathologies, the ECG aspects at rest and during exercise, and the anatomy of the malformation observed at the CCTA.

As regards functional studies and in a future perspective, hybrid CCTA/SPECT myocardial perfusion imaging [36], as well as CT assessment of fractional flow reserve (FFR) [37, 38], could play a relevant role in risk stratification of subjects with CCAA, but evidences and large studies are still lacking to allow solid conclusions and to establish precise reference parameters.

7.4 Myocardial Bridge

An emerging problem is the intra-myocardial or "tunnelled" course of a coronary artery, a congenital anomaly known as a *myocardial bridge* (MB). In autopsy studies on the general population, the prevalence of MB ranges from 5 to 86% [39],

while in studies based on coronary angiography, it drops to 0.5–12% and up to 40% (if provocative tests are performed).

With the advent of CCTA, an MB is diagnosed in vivo with a frequency even higher than in the coronary angiography, and its identification poses problems as regards risk stratification. The intramyocardial course of a coronary artery, in particular, the LDA, was associated with some cases of exercise-related SCD [1, 2, 40]. This phenomenon was reported 40 years ago by Morales et al. [41], but subsequently, it was questioned, given the remarkable frequency with which an MB is found at the autopsy in subjects deceased for other reasons [42, 43].

An MB is a condition in which a more or less long tract of a major coronary branch, instead of running on the epicardial surface, *tunnels into the myocardium*, being surrounded by a ring or sleeve of muscle fibres which contracting in systole causes an ab-extrinsic "strangulation" of the artery ("milking effect"). This phenomenon can be accentuated during exertion, especially if the effort is intense and it has an abrupt, not gradual, beginning (Fig. 7.4), in relation to the increase in cardiac contractility and to the shortening of the diastole (in which most of the coronary flow physiologically occurs) [44–46], a mechanism responsible for myocardial ischemia, especially in subjects with "extreme" myocardial hypertrophy or worse a hypertrophic cardiomyopathy. The extensive use of CCTA has radically changed the approach to the problem [47–50]. The most relevant points emerging can be summarized as follows:

- *The prevalence of an MB is much greater* than we have hitherto assumed. It affects mostly the LDA (especially its middle tract), rarely a diagonal branch and the CX. The high prevalence of an MB in asymptomatic subjects has led the authors to attempt a classification with a clinical prognostic value. Kim et al. initially distinguished the MBs on the LDA in two types: with *partial* (or incomplete) or *total* (or complete) artery entrapment [47]. Subsequently, the MBs were distinguished in *superficial and deep*, using as a cut-off value for the thickness of myocardium overlying the trapped artery by at least 2 mm [47, 48].
- *The ab-extrinsic artery compression*, assessed by CCTA or coronary angiography, is a crucial aspect in prognostic evaluation. In a significant MB, artery compression is easily appreciable in systole, but studies with intravascular ultrasound (IVUS) have shown that the compression extends up to the beginning of diastole compromising coronary flow beyond systole [51, 52]. More recently, several hemodynamic alterations and endothelial dysfunctions leading to impairment in coronary blood flow in both phases of the cardiac cycle were identified [40].
- *Other determinants of prognosis are the length and depth of the intramural tract* [44], which can now precisely assess by CCTA. Reasonably, 2–3 cm in length and a depth >2 mm can be considered a cut-off of potential malignancy regardless of symptoms or signs of inducible ischemia. MBs superficial and/or localized on distal or secondary branches should be considered benign unless their direct responsibility for symptoms and signs of myocardial ischemia is clearly assessed.
- While the intramural tract is spared, the one immediately proximal to the MB is affected with increased frequency (up to 90%) by *atherosclerotic lesions*, which affect the long-term prognosis [39, 51]. This is particularly important in master athletes.

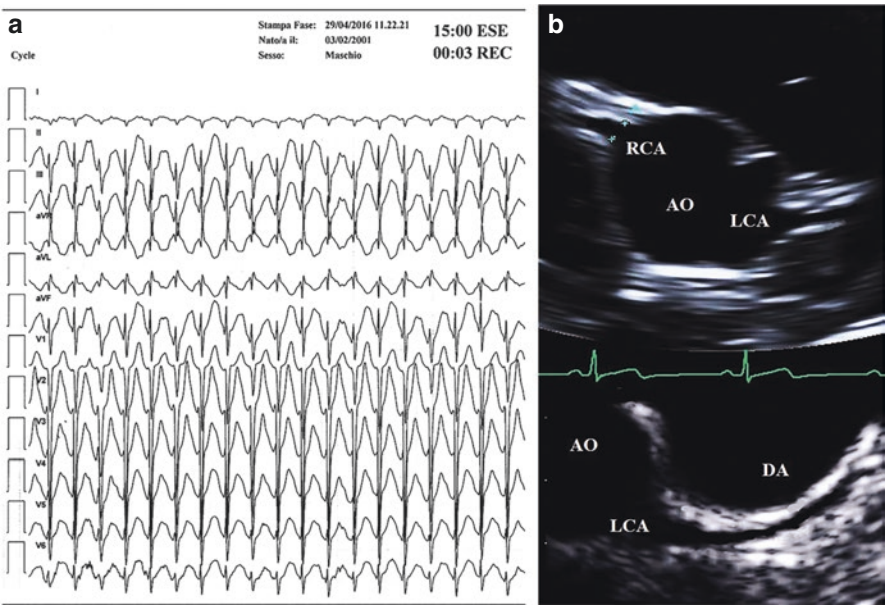

Fig. 7.4 A 16-year-old competitive soccer player (Junior Team Serie A). Episodes of prolonged palpitation with chest tightness and cold sweating during a match, which forced him to leave the field. He was transported to the emergency room of an important hospital in Milan. An MRI and an electrophysiological study were promptly made with "negative" results, and he was discharged with authorization to resume soccer. The team doctor sent him to us for a second opinion. Maximal stress ECG was negative (**a**), except for mild chest tightness at the peak effort. The origin of the right (RCA) and left coronary artery (LCA) at transthoracic ECHO (**b**) was normal (AO, aorta; DA, descending artery). However, during Holter recording with a training session, after a few sprints of running, the young suddenly stops complaining of severe chest discomfort and lies down on the ground pale and cold sweating. Due to clinical symptoms, a CT coronary angiography was performed. It confirmed the normal origin of coronary arteries (**c**) but revealed a deep myocardial bridge on the left descending artery (**d**, **e**, white arrow). Note the similar picture (**f**) obtained by transthoracic ECHO (subcostal, off-axis view). The obstructive nature of the myocardial bridge was confirmed by coronary angiography (**g**). A successful surgical "*debridging*" was performed by Prof. Marco Pozzi, "Le Torrette" Hospital-Ancona, bringing the artery back to the epicardial surface (**h**, **i**, white arrow). After a year of rehabilitation and training, the young return to play soccer with absolutely no symptoms

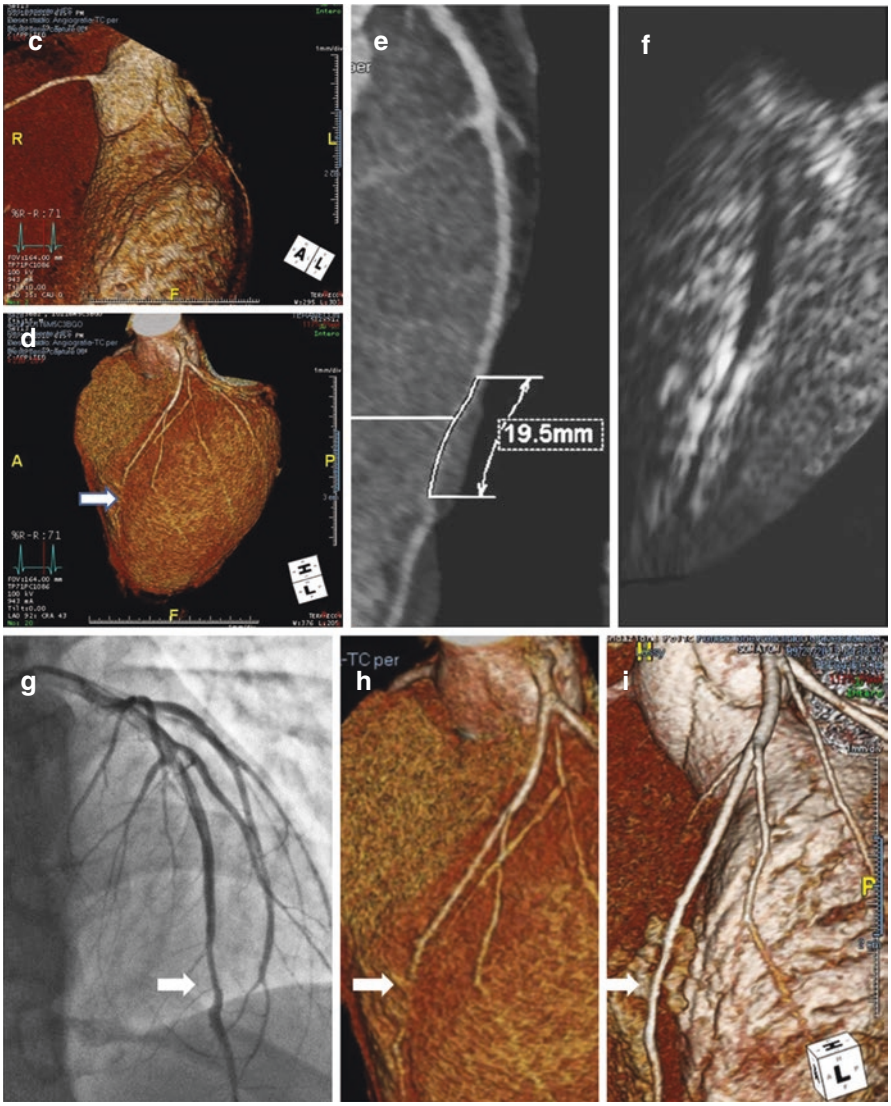

Fig. 7.4 (continued)

– New CCTA-derived techniques as fractional flow reserve (FFR) [36, 37] and intracoronary transluminal attenuation gradient [53] opened new perspectives and probably will become a standard as regards risk-stratification in subjects with MB, but to date, further and specific studies are needed to allow conclusive evidences.

7.5 Coronary Fistulae

Coronary fistulae (CF) are characterized by the communication between the coronary system and the heart chambers, representing a congenital persistence of the intra-trabecular spaces and embryonic sinusoids. Coronary flow is diverted to a heart chamber, a large vessel or other structure, bypassing the myocardial capillary network. CF vary greatly in morphological appearance and clinical presentation: most originate from the RCA or from the LDA, as a single communication, but multiple CF are not uncommon [54–56]. Myocardial blood flow is usually not compromised, and shunt through the fistula, present in more than 90% of cases, is often of modest entity. Small CFs, usually single, mostly originating from the LDA and terminating in the pulmonary artery, generally do not give signs, symptoms or complications and are usually considered benign.

Despite the rarity, the problem cannot be neglected by the cardiologists and sports physicians because, although most CF are benign and allow to practice all sports, there is a small percentage of subjects with potentially malignant fistulae, typically large and/or multiple. Myocardial ischemia may result from two mechanisms: a persistent or episodic steal of blood flow from the normal coronary branches to the competing fistulous low-pressure tract and/or stenosis and obstruction of side branches secondary to thrombus formation related to ulceration and atherosclerosis in the anomalous coronary artery [57].

Transthoracic and trans-oesophageal ECHO can facilitate the identification of the origin and point of insertion of the CF, but diagnostic confirmation by means of CCTA [58, 59] and, if necessary, by coronary angiography, which should be reserved for symptomatic cases or with strong suspicion of exercise-induced ischemia. Large and/or multiple CFs, causing ischemia, require percutaneous [60, 61] and/or surgical closure (ligation) [62], which yield essentially the same results.

7.6 Acquired Anomalies

Regular moderate physical activity reduces all-cause mortality and improves long-term cardiovascular health [3]. In contrast, strenuous efforts may increase the risk of adverse cardiac events, especially in middle-aged and older athletes (master) [4]. Master athletes (MA) are a considerably growing population [63], in which the most frequent cause of SCD during exertion is *coronary atherosclerosis* (CA) [5, 6], both as a complication of a severe obstructive disease [6, 7] and rupture/erosion of unstable non-obstructive plaques [4, 63].

Although less frequently, CA is responsible for SCD even in young athletes, especially if genetically predisposed [1, 2, 64]. In these cases, the plaques show peculiar characteristics, being fibrous with neointimal smooth muscle cell hyperplasia, a preserved tunica media and with the absence of acute thrombosis [65]. Other rarer acquired coronary lesions responsible for exercise SCD in this population are the *Kawasaki disease* and regular use (abuse) of *cocaine*.

7.6.1 Coronary Atherosclerosis

Coronary atherosclerosis (CA) is a leading cause of death in all countries [66]. It has an inflammatory nature [67] and leads to a progressive occlusion of the coronary arteries by "plaques" which can have different characteristics and compositions (low-density lipoproteins, calcium, smooth muscle cells, macrophages). The disease can manifest with acute or chronic coronary syndromes, myocardial infarction and SCD [68]. Genetic, environmental and lifestyle factors interact in determining the clinical phenotype of the disease [64].

In the previous century, based on autoptic features of famous marathon runners who died for other reasons [69], it was hypothesized that they were immune from CA (the Bassler hypothesis) [70, 71]. Subsequent works [15, 72] provided support for this hypothesis suggesting that aerobic exercise is in any case protective against myocardial ischemia [72–74]. However, in the late 1970s, it was reluctantly accepted that not all marathoners were free of CA as some died because of it during the race [75–77]. The advent in this century of CCTA changed everything, showing that CA is not so uncommon in asymptomatic middle-aged marathon runners [78, 79]. Therefore, the relationship between CA and sports activity must be seen from two different points of view:

- *Physical activity is recommended in primary (and secondary) prevention of* CA [80]. This should prompt us to encourage apparently healthy individuals, especially those with coronary risk factors, to undertake moderate, recreational physical activity on a gradual and regular basis;
- *More and more subjects of adult and advanced age* devote themselves to intense, recreational and competitive sports activities, often without adequate training and an appropriate cardiovascular preparticipation screening [81].

In other words, regular exercise not only protects the heart but also can damage it ("*physical exercise paradox*") [82–85]. This ambivalent effect, however, is only apparent. The beneficial effect of regular physical training, in fact, develops over the long term. Conversely, the risk of acute coronary events is linked to the neurometabolic changes induced by a burst of intense exercise in subjects at risk and/or inadequately trained.

Evidence for a cause-effect relationship *between exercise and acute coronary events* was first well documented in the 1990s [83, 84] and later confirmed [85–89]. All the studies have highlighted that *the risk is clearly higher in subjects who do not practice regular physical activity*, while it is significantly lower in those who practice it regularly. A similar "paradoxical effect" of exercise was observed also for

SCD in MA over the age of 30–40, in most cases associated with the presence of silent CA [90].

The absolute risk of acute cardiac (coronary) events, however, was very low [7, 83–90]. Numerous mechanisms have been proposed to explain this. Exercise causes platelet activation in patients with CA already at low workloads [91]. In trained subjects, also enrolled in a moderate physical activity program, exercise platelet activation is reduced or absent [92]. In addition, regular physical activity is associated with reduced sympathetic activity and enhanced vagal activity, thus determining a favourable and protective autonomic balance [93]. Finally, *due to the possible role of inflammation in acute coronary processes*, among the protective factors of regular physical exercise, its ability to modify the "inflammatory" profile of the organism should also be included, causing a reduction in the cytokines produced by leukocytes and a decrease in C-reactive protein [94].

More recently, attention was focused on *the number and composition of atherosclerotic plaques, as well as on vascular remodelling*. Plaques, even non-obstructive, leading to acute coronary events typically show "positive vessel remodelling" (PVR) and "low attenuation" (LAP) [95]. Very interestingly, the ultramarathon races and the resulting "inflammation" increase the volume (swelling) of pre-existing plaques [96]. Finally, marathon runners, despite having less risk factors than sedentary people, can have on CCTA the same number (and a greater total volume) of plaques, calcified and non-calcified [78].

From what has been said, the need for a thorough medical evaluation of competitive master athletes (MA) practising sports with high cardiovascular demand (marathon, cycling, etc.) seems beyond question. Medical evaluation should aim at identifying those with silent ischemic heart disease and a greater risk of acute coronary events triggered by physical activity.

In our opinion, *a maximal stress ECG test is "strongly" recommended in MA* with a moderate/high cardiovascular risk profile (see below), such as in males over 40–45 years of age and in women of age over 50–55 with one or more coronary risk factors [81]. There are numerous scoring systems or risk cards that help us to define the individual risk of cardiovascular events (such as the European Society of Cardiology "SCORE") [97]. The stress ECG test, however, has a low sensitivity and specificity in subjects with a low pre-test probability of the disease. In our experience, better sensitivity and specificity than stress ECG test alone can be obtained by *the cardiopulmonary exercise test (CPET),* although it requires more equipment and a specific experience of cardiologists [98–101].

In a recent work [102], we analysed the role of risk factors, symptoms and CCTA in a large group of MA with suspected inducible myocardial ischemia. Our data suggest that, when symptoms and/or equivocal or positive stress ECG tests are present, the ESC risk score is a good indicator for the presence of moderate-severe CA on the CCTA. We proposed a first algorithm *for ruling out CA and/or other coronary anomalies (congenital) potentially responsible for ischemia*. We recommended a CCTA in the presence of one or more of the following aspects:

1. Symptoms during/immediately after effort: chest pain/discomfort, presyncope/syncope (Fig. 7.5)

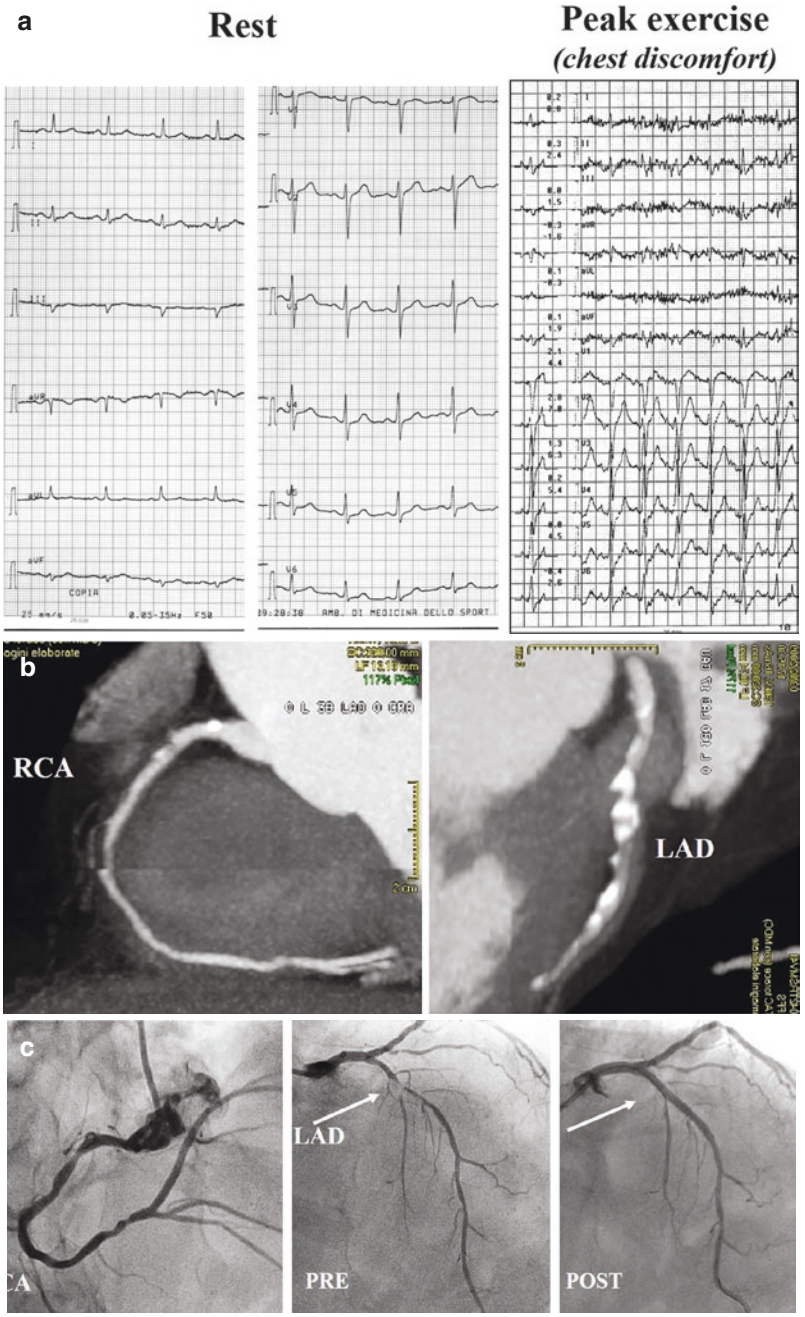

Fig. 7.5 A 63-year-old marathon runner. Recent onset (2 months) of chest "discomfort" only when running uphill. (**a**) He has a similar symptom at the peak of a negative stress ECG test. The symptom rapidly regressed in the recovery phase. (**b**) CCTA showed diffuse atherosclerotic non-obstructive plaques in the right coronary artery (RCA) and severe obstructive lesions in the left anterior descending artery (LAD), confirmed on coronary angiography (**c**, PRE) and successfully treated with angioplasty and stent (POST)

2. Equivocal stress ECG test plus at least one among the following: (a) male sex or female at postmenopausal age; (b) risk factors (singularly or in association) as hypertension, hypercholesterolemia, BMI > 25 and positive family history for myocardial ischemia or SCD; (c) risk score > 1% at 10 years; and (d) symptoms
3. Positive stress ECG test in asymptomatic subjects with low or intermediate risk score (Fig. 7.6)
4. A very high risk score (>10%), even in the absence of ECG abnormalities and symptoms

In MA with positive stress ECG test, symptomatic and/or with high/very high risk score, *coronary angiography is reasonably the first choice*.

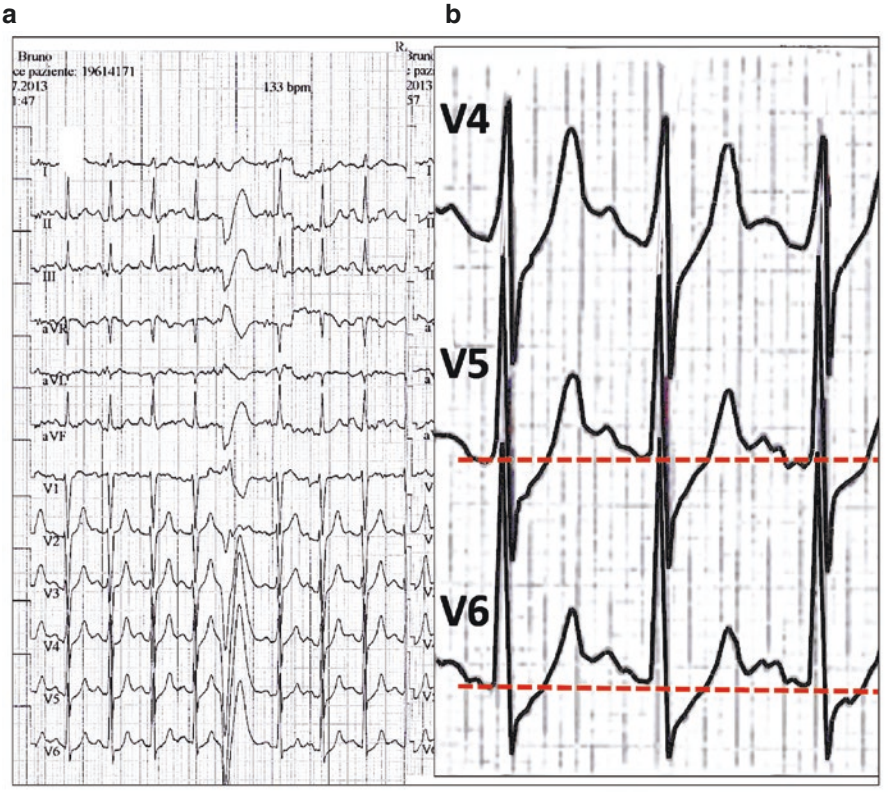

Fig. 7.6 A 64-year-old master athlete very passionate about mountain biking. Palpitations during the most demanding climbs. (**a**) Maximal stress ECG test considered as "negative" by cardiologists but at least equivocal on a closer inspection (**b**). He had been a smoker since his youth and hypercholesterolemic since the age of 40. (**c**) The CCTA revealed atherosclerotic plaques on the left anterior descending artery (LAD) and intermediate branch (arrow). We strongly advised him against continuing cycling at a competitive level without being heard. (**d**) Two years later, after a very demanding climb (on mount Terminillo, 2217 m high), he had severe acute chest pain lasting 30 min. Transported to the hospital, clinical examinations and coronary angiography confirmed an acute coronary syndrome from sub-occlusion of the intermediate branch (arrow)

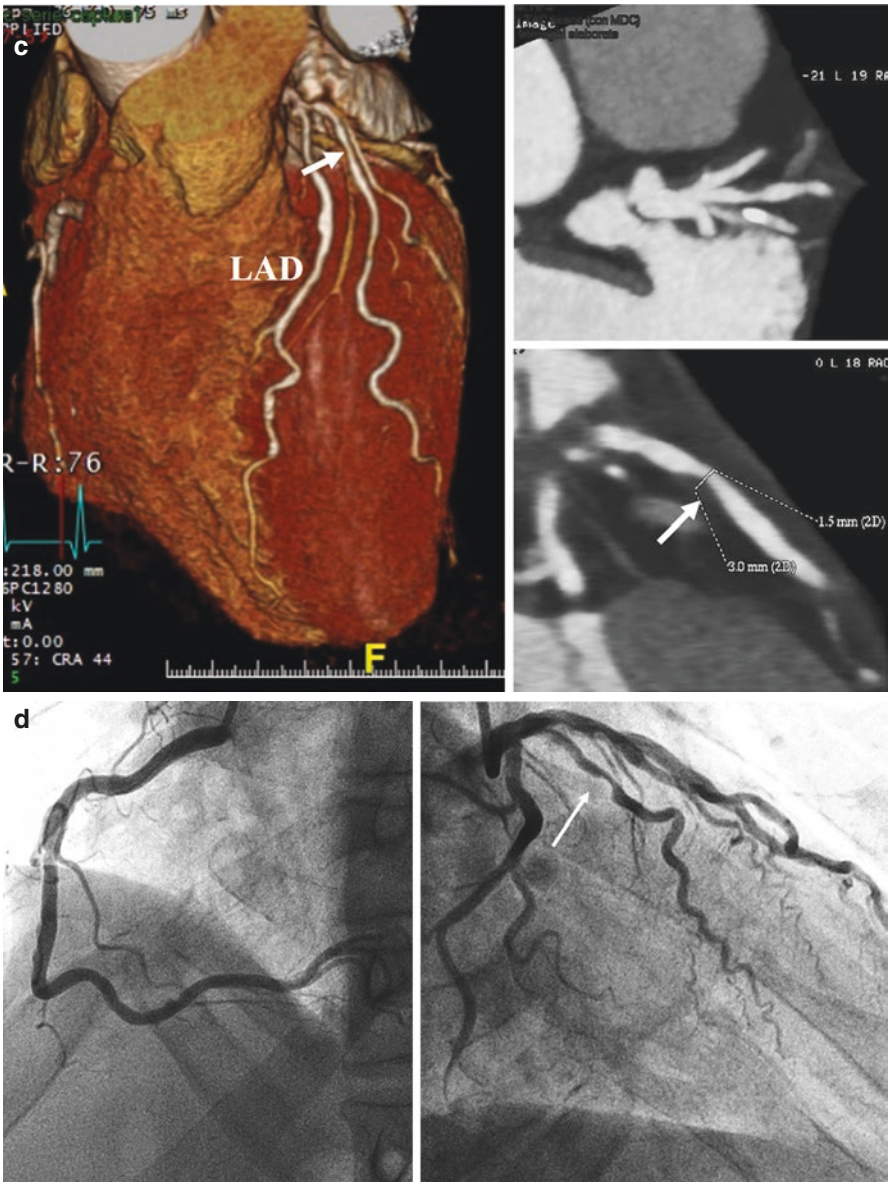

Fig. 7.6 (continued)

In the second algorithm, we explained our approach for managing sports activity in MA with evidence of CA at the CCTA. In general, we considered not eligible for competitive sports with high cardiovascular demand all MA with any degree of CA (Fig. 7.6), and we proposed a safer non-competitive sports activity, preferably aerobic and "dosed" according to clinical findings and functional capacity [97–103].

In asymptomatic MA with mild CA, we allowed all non-competitive sports after appropriate control/correction of risk factors, prescribing medical treatment when necessary. In MA with moderate CA and/or symptoms, we proposed further investigations: myocardial scintigraphy if they had mild CA and were symptomatic or they were asymptomatic with a coronary obstruction between 30 and 50% and a coronary angiography in the other cases.

In case of severe or moderate CA plus symptoms of ischemia at the scintigraphy, we discouraged any physical exercise and proposed coronary angiography. If coronary angiography did not show the necessity of treatment, we allowed controlled physical training (under qualified medical supervision), together with control/correction of risk factors and medical treatment when appropriate. On the contrary, if invasive treatment is needed, we proposed a re-evaluation after it, following the same criteria.

The state of physical and mental well-being associated with physical activity is an element that must always be kept in mind in the management of MA with CA, since the doctor's goal must be not only to extend their survival but also to improve their survival and the quality of life.

7.6.2 Kawasaki's Disease

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is an acute, paediatric, self-limiting vasculitis of unknown aetiology (probably viral) [104]. Approximately 20% of untreated children and 4% of those treated with intravenous gamma-globulins develop *coronary artery aneurysms*, which can be complicated by progressive coronary stenosis, myocardial infarction and SCD [105].

Evolution of coronary lesions over time is documented. Patients with *no evidence of lesions* (diffuse/segmental dilation of one or more major coronary branches) at any stage of the disease appear to have the same risk of cardiac events as the general population over the next 20 years [106]. Conversely, in subjects with lesions at any stage of KD, structural and functional abnormalities of the coronary arteries appear to persist even when they return to the normal calibre [107]. If aneurysmal lesions do not regress, stenosis or occlusion may subsequently develop, increasing the risk of myocardial ischemia [108, 109].

The eligibility criteria for sporting activity in an adolescent who suffered from KD depend on the involvement of the coronary arteries. Of course, a sedentary life will be discouraged, but care is needed to decide which type and intensity of sport to allow.

Children/adolescents with no involvement or only a slight transient ectasia of the coronary arteries will be able to carry out any type of sporting activity after at least 6 months from the complete clinical recovery. Those with coronary aneurysms documented in the acute/subacute phase can play sports with moderate cardiovascular engagement; provided that the coronary arteries have returned to normal calibre, there is no evidence of ischemia at the maximal stress ECG test and/or at the myocardial perfusion imaging. Similar considerations should apply (with more attention) to patients in whom persistence of small isolated aneurysms.

Competitive sports activity will be avoided in patients with large and/or multiple aneurysms, with or without obstruction to the coronary flow, previous myocardial infarction, exercise-induced ventricular arrhythmias, and in those requiring anticoagulant or antiplatelet therapy. From what has just been said, it is evident that the evaluation of the calibre trend of the coronary branches must be entrusted to expert sonographers and can benefit from an in-depth study using CMR angiography (in children) and CCTA in adolescents and young adults.

7.6.3 Cocaine-Induced Coronary Disease

Cocaine is a drug widely used at all ages, especially in the young. Its effects show great inter-individual variability due not only to genetic factors but also to the way of intake, the amount absorbed and the possible presence of concomitant cardiovascular diseases which can favour fatal events [110, 111]. Complications of acute and chronic use of cocaine, sometimes severe, concern the *central nervous system* (hyperthermia, ischemic/haemorrhagic events, etc.) [112–114] and *the respiratory system* (pneumothorax, bronco-obstructive crises, respiratory arrest, etc.) [115], but *the most serious and frequent are those affecting the cardiovascular system* [114]. The effects of cocaine on the heart are both direct and indirect.

At higher dosage, *cocaine blocks fast sodium channels*, in a way similar to that of type-I antiarrhythmic agents (procainamide) with a potential a pro-arrhythmic effect. *Tachycardia* is partly due to a central action [116] and to the *increase in circulating and intramyocardial levels of catecholamines*, both at rest and during exertion. In cultures of spontaneously contracting myocardial cells, cocaine and noradrenaline have a synergistic, dose-dependent toxic effect, which ultimately results in the cessation of contractile activity and cellular destruction with hypercontraction-disorganization phenomena of the cytoplasm, theoretically comparable to the myocardial contraction bands.

Cocaine has a generalized and focal vasoconstrictive action which explains the increase in systolic and diastolic blood pressure both at rest and during exercise and the left ventricular hypertrophy secondary to *hypertensive state* often present in young subjects [114]. Cocaine significantly reduces the diameter of epicardial and endocardial vessels by direct vasoconstrictive action [117, 118], with focal spasm that can occur in healthy coronary segments [119] as well as in those with significant organic stenosis [120], and regresses with the exhaustion of the effects of the substance. It is possible that an imbalance of the adrenergic system similar to that responsible for the Prinzmetal's angina also contributes to the coronary vasospastic effect, and a dysfunction of the coronary microcirculation has also been hypothesized [121]. Finally, an influence of the drug on the course of CA has been suggested as a factor favouring intimal proliferation and endothelial cell dysfunction [122, 123]. These mechanisms, alone or in combination, may explain the high prevalence of *coronary aneurysms* (almost 30%) in *chronic cocaine users* [124].

Despite the lack of retrospective and prospective studies (very difficult to do!), it is entirely reasonable to say that *recreational or competitive sportspeople who abuse cocaine are at higher risk for sports-related SCD*.

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Interpretation and Diagnostic Workup of Premature Ventricular Beats

8

Riccardo Vio, Domenico Corrado, and Alessandro Zorzi

8.1 Introduction

The risk of sudden cardiac death (SCD) among athletes is associated with a pathological substrate that, in the presence of specific triggers such as intense physical activity, can predispose to life-threatening ventricular arrhythmias [1].

The documentation of premature ventricular beats (PVBs) at 12-lead ECG or ambulatory ECG can raise the suspicion of an underlying cardiac disease. PVBs with common morphologies are considered to be benign, including infundibular or fascicular ectopic beats, but others represent a red flag for a pathological substrate and must be properly investigated. [2–4]

Based on recent evidence, this chapter focuses on the PVBs interpretation in the athlete with particular reference to uncommon potentially malignant PVBs and appropriateness of cardiac magnetic resonance (CMR) imaging to rule out or rule in an at-risk myocardial substrate.

8.2 The Concept of "Common" and "Uncommon" PVBs

Modern criteria of ECG interpretation in the athletic population divide abnormalities into two categories: "common" and "uncommon." [5, 6] The former group includes, for example, the early repolarization pattern, encountered in a wide range of athletes but rare as an isolated ECG marker of an underlying heart disease. Other

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abnormalities like lateral T wave inversion are reported only in a minority of healthy athletes and therefore must trigger additional testing to exclude some form of cardiomyopathy.

With a similar approach, classification of PVB characteristics has been proposed: "common" PVBs are those frequently encountered in athletes with idiopathic ventricular ectopy, whereas "uncommon" PVBs are more often associated with myocardial alterations (Table 8.1).

The most important feature of the PVBs is morphology. Young athletes with benign and idiopathic PVBs most often show a morphology suggesting a right or left ventricle outflow tract origin (left bundle branch block—LBBB—like with vertical axis) or, mostly in prepuberal children, from the fascicles of the left bundle branch (narrow QRS < 130 ms, incomplete right bundle branch block—RBBB—like plus hemiblock) [7, 8]. Those PVBs are usually numerous and isolated and tend to decrease during effort [9].

PVBs with LBBB like morphology and intermediate or superior axis (that originates from the right ventricle or interventricular septum), together with those with RBBB like morphology and wide QRS (particularly with a superior axis that indicates a left ventricle lateral wall origin), may be the expression of an underlying cardiomyopathy. If the arrhythmia increases in number or complexity during effort, the suspect is reinforced [8, 10–12].

Table 8.1 PVB classification according to the probability of underlying myocardial pathological substrate

QRS morphology	Probable origin of PVB	Disease probability
Common patterns in athletes		
LBBB with late precordial transition (R/S = 1 after V3) and inferior axis	Right ventricular outflow tract	Usually benign
LBBB and inferior axis but with small R-waves in V1 and early precordial transition (R/S = 1 by V2 or V3)	Left ventricular outflow tract	Usually benign
Typical RBBB with superior axis and QRS <130 ms	Left posterior fascicle of the left bundle branch	Usually benign
Typical RBBB with inferior axis and QRS <130 ms	Left anterior fascicle of the left bundle branch	Usually benign
Uncommon patterns in athletes		
Atypical RBBB, QRS ≥130 ms, positive QRS in V1-V6 and inferior axis	Anterior mitral anulus	Few data, probably usually benign
Atypical RBBB, QRS ≥130 ms, intermediate or superior axis	Posterolateral mitral valve annulus, papillary muscles or left ventricular free wall	May be associated with myocardial disease
LBBB with superior or intermediate axis	Right ventricular free wall or interventricular septum	May be associated with myocardial disease

LBBB left bundle branch block, *RBBB* right bundle branch block
Reproduced with permission from [4]

The evaluation of athletes with PVBs must include also a careful medical history, because a positive personal history for syncope or familial history of SCD further increase the chance to detect a cardiac disease, and resting ECG which may show pathological findings such as repolarization abnormalities.

Lastly, recent studies have questioned the traditional concept that the risk of cardiac disease is related to the "arrhythmic burden" (i.e., the higher the number of PVBs, the greater the risk), so that it is no more advisable to consider the number of PVBs at the stress ECG test or at the ambulatory ECG as a criterion to prescribe further diagnostic testing [4].

8.3 Pathological Substrates in Athletes with PVBs

Several cardiac conditions can be associated with PVBs, ranging from ischemic to hypertensive cardiopathy, not to mention cardiomyopathies and congenital diseases. Most of them can be reasonably excluded on the basis of first- (history, physical examination, and ECG) and second-level testing (stress ECG test, ambulatory 24-hour ECG recording, and echocardiogram). However, the diagnosis of some arrhythmic substrates may be missed unless additional investigations are used. Among these entities, the most important ones are the "left ventricular nonischemic scar" and the "catecholaminergic polymorphic ventricular tachycardia."

A nonischemic left ventricular can be documented by CMR imaging as late gadolinium enhancement in the subepicardial/midmural layer of the left ventricular free wall (commonly the inferior-lateral wall). Such lesions differ from the ischemic ones because they do not affect the endocardium. Since the endocardium is the layer that contributes the most to myocardial contractility, no (or only mild) regional abnormalities are identifiable at the echocardiogram. Historically, the nonischemic left ventricular scar has been considered as the result of a previous myocarditis. Nowadays, there is mounting evidence that specific genetic mutations can determine their formation; additionally, they appear more prevalent in athletes than in sedentary controls, and sport-related damage is also conceivable. No matter the cause, the nonischemic left ventricular scar has a marked clinical relevance because it represents a potential substrate of macro-reentrant ventricular tachycardia [13–16].

Catecholaminergic polymorphic ventricular tachycardia is a genetic disease affecting the ion channels leading to an increased inward of calcium ions in the myocyte following an adrenergic stimulation. The typical manifestation is the appearance of polymorphic PVBs at the stress ECG test (both RBBB- and LBBB-like), which increase in number and complexity at a higher workload. The heart is structurally normal; therefore, such arrhythmic presentation must be investigated with genetic testing aimed to identify genetic mutations in the ryanodine receptor and calsequestrin genes [17].

In master athletes, aged 40 years old or more, the most important arrhythmic substrate is coronary artery disease: PVBs typical of ischemic patients have an

"R on T" pattern and aggregate themselves in run of non-sustained ventricular tachycardia at the stress ECG test.

8.4 Recent Evidence on Ventricular Ectopy in Athletes

The rising interest in the field of PVBs in athletes has been triggered by the wide-scale application of CMR in the last decade. This examination, initially performed to rule out an arrhythmogenic cardiomyopathy, led to the discovery of isolated non-ischemic left ventricular scar as the origin of PVBs in some cases that would have been otherwise considered idiopathic.

The first authors to describe the nonischemic left ventricular scar in the athlete were Schnell et al. in 2015, who described a group of seven individuals who were referred to CMR imaging for repolarization abnormalities and/or unexplained arrhythmias at the stress ECG test. Even though not emphasized by the authors, the peculiar aspect of the exemplifying figures in the paper was the onset of repetitive PVBs with RBBB like morphology, wide QRS, and superior axis, triggered by the physical exercise [16].

The following year, we published a broader case series of 35 athletes with PVBs and nonischemic left ventricular scar [14]. The study underscored that the CMR was performed only in a minority of patients for ECG (lateral T wave inversion and/or low QRS voltages) or echocardiographic (lateral wall hypokinesia) abnormalities; the others underwent CMR imaging specifically for apparently idiopathic ventricular arrhythmias. In the majority of cases, the PVB morphology was RBBB-like, wide QRS and superior axis, consistent with an origin from the left ventricular lateral free wall (Fig. 8.1). Noteworthy, during a mean follow-up of 38 ± 25 months, six (22%) individuals suffered major arrhythmic events such as appropriate defibrillator shock, sustained ventricular tachycardia, or SCD. In five out of six cases, the arrhythmic event occurred during sport activity, underscoring that arrhythmias in the left ventricular nonischemic scar are driven by adrenergic stimulation.

Additional evidence was provided by Di Gioia et al. who published an autoptic series of young subjects who died suddenly [18]. Left ventricular nonischemic scar was rare in those who died at rest but was the most common finding in those died while practicing sport (25% of case), and in such cases, the scar was always associated with fibroadipose replacement spots in the right ventricle: this findings suggest that the left ventricular nonischemic scar might be an epiphenomenon of a left-dominant arrhythmogenic cardiomyopathy rather than a prior myocarditis. A similar case is that of a famous Italian footballer who died suddenly during competition [19].

The knowledge in the field was broadened by a study that analyzed a series of athletes referred to a tertiary center for PVBs evaluation and CMR imaging [20].

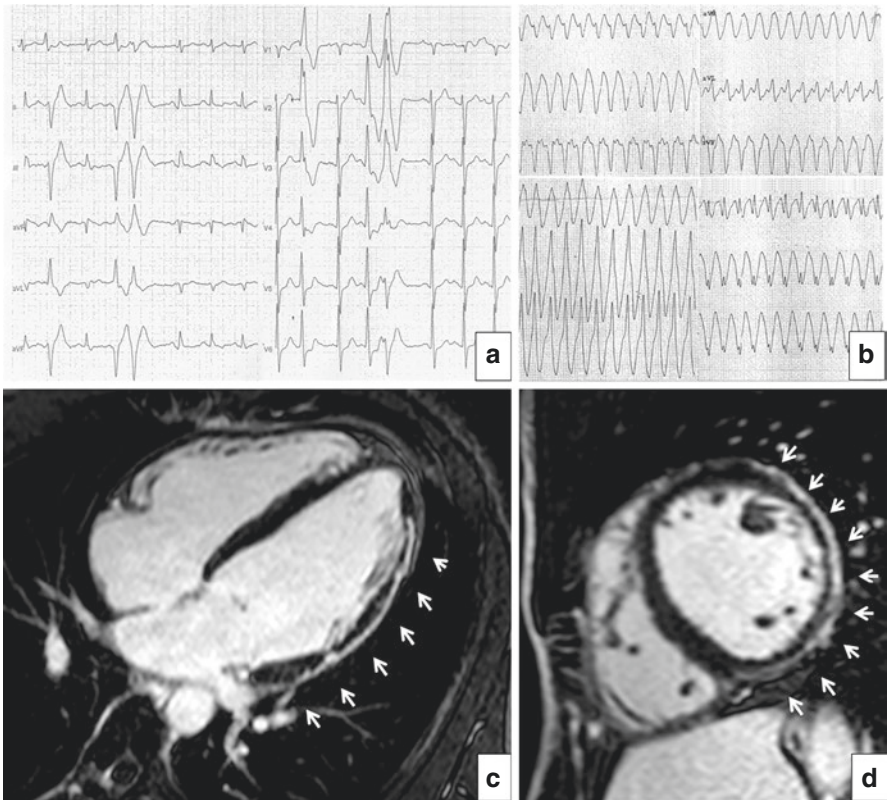

Fig. 8.1 A 42-year-old martial art player presented with frequent and coupled premature ventricular beats with right bundle branch block/superior axis morphology during exercise testing (**a**). The athlete experienced sustained VT during follow-up (**b**). Postcontrast sequences on contrast-enhanced CMR, four-chamber view (**c**), and short-axis view (**d**) revealed a subepicardial/midmyocardial "stria" of LGE involving the anterolateral, lateral, and infero-lateral LV wall consistent with post-inflammatory myocardial fibrosis. (Modified and reproduced with permission from [14])

Late-enhancement prevalence was three times higher in subjects with PVBs that persisted or worsened during stress test compared to those with a reduction on PVBs burden at increasing workload (47% vs 17%). The RBBB-like morphology of PVBs and the presence of negative T waves on resting ECG were the other independent predictors of pathological substrate (Fig. 8.2).

In another study aimed to evaluate the PVB burden in young athletes through a 24-h ECG Holter including a training session, 17 had frequent (>500/day), repetitive, or training-induced PVBs and underwent CMR [13]. In three cases, the CMR demonstrated a left ventricular nonischemic scar: all three athletes showed

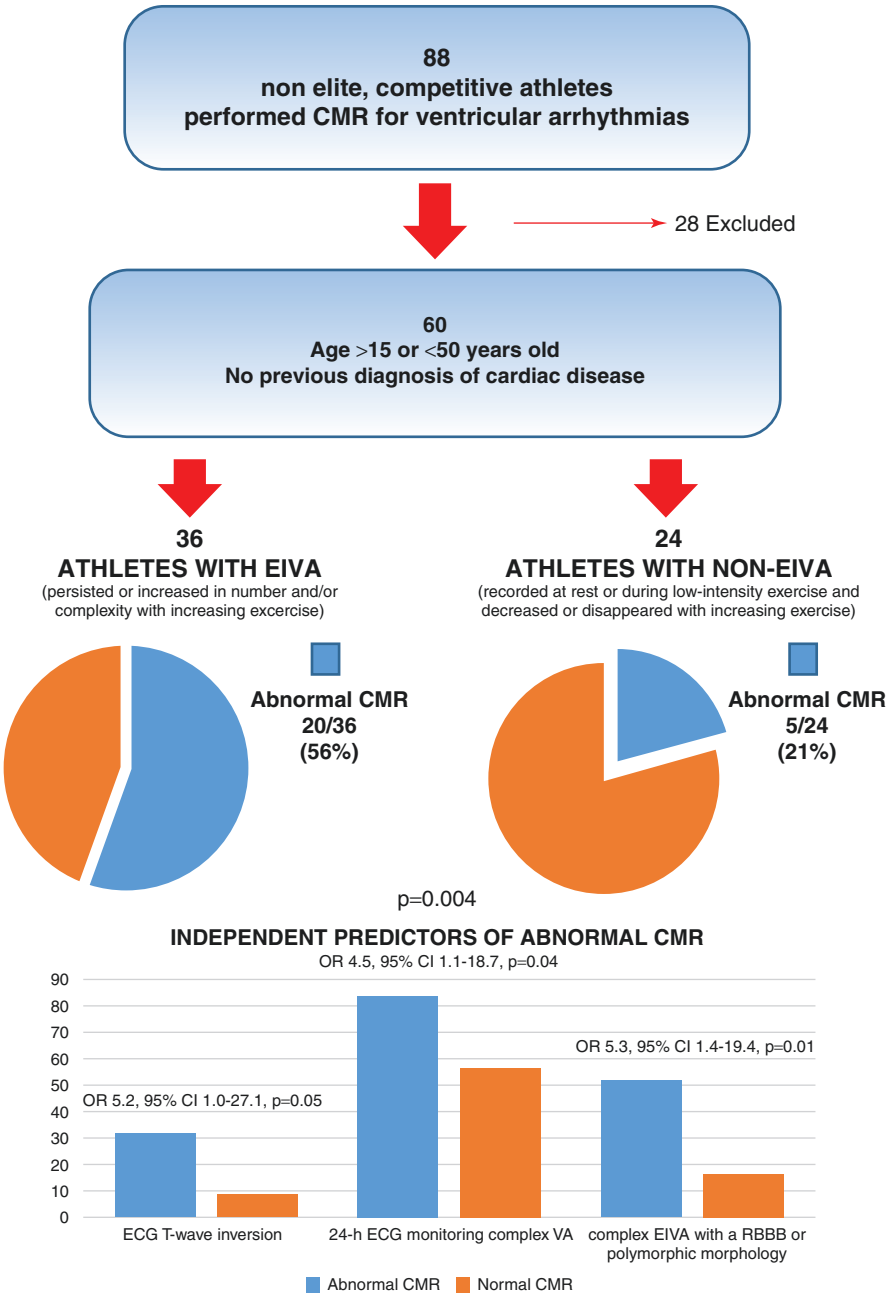

Fig. 8.2 Summary of main study findings. *CMR* cardiac magnetic resonance, *EIVA* exercise-induced ventricular arrhythmias, *ECG* electrocardiogram, *VA* ventricular arrhythmias, *RBBB right bundle branch block*. (Reproduced with permission from [20])

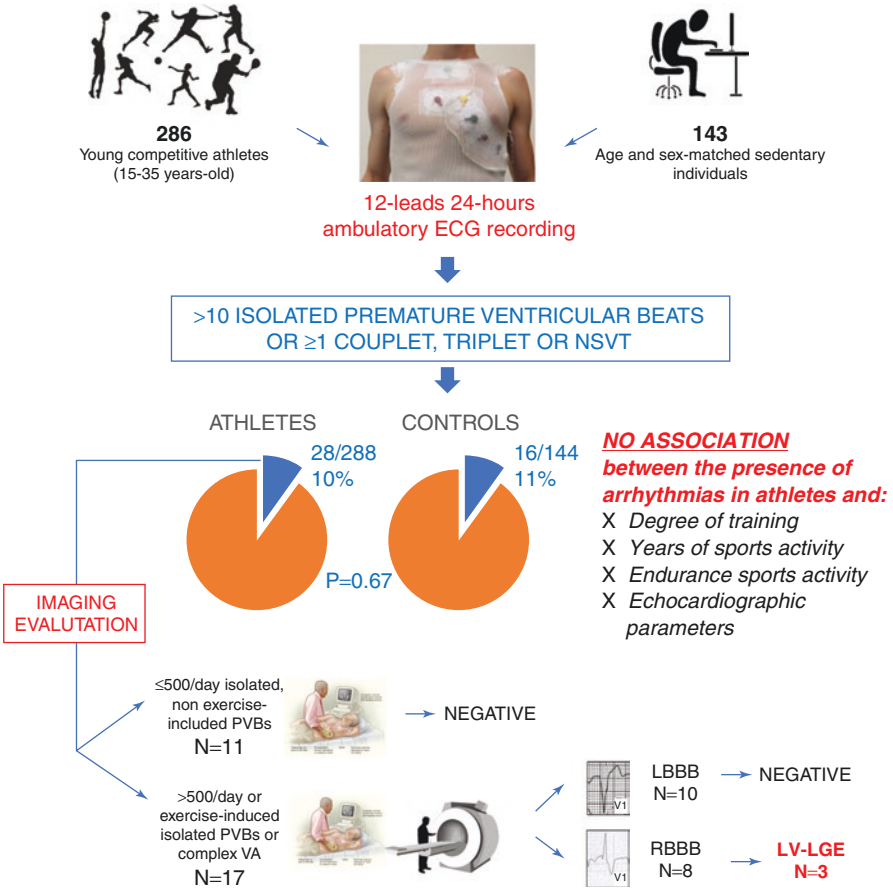

Fig. 8.3 Summary of the study methods and main findings. *LBBB* left bundle branch block, *LGE* late gadolinium enhancement, *LV* left ventricular, *NSVT* non-sustained ventricular tachycardia, *PVB* premature ventricular beat, *RBBB* right bundle branch block, *VA* ventricular arrhythmia. (Reproduced with permission from [13])

PVBs with RBBB-like morphology and inferior axis triggered by the exercise (Fig. 8.3).

The systematic evaluation of athletes with at-risk characteristics PVBs was proved to further refine the diagnostic sensitivity of the preparticipation screening [21]. Adding the stress ECG test to classic first-line investigations (history, physical examination, and 12-lead ECG) yielded to a 75% increase of diagnosis of pathological cardiac substrates (mainly left ventricular nonischemic scar) in a population of 10,985 young athletes. The remarkable result was counterbalanced by a 20% reduction of positive predictive value of the preparticipation screening (i.e. increase in false positives and unnecessary further investigations) (Fig. 8.4).

Finally, in a multicenter Italian studies reporting on 251 competitive athletes with negative family history, normal ECG, and echocardiogram who underwent

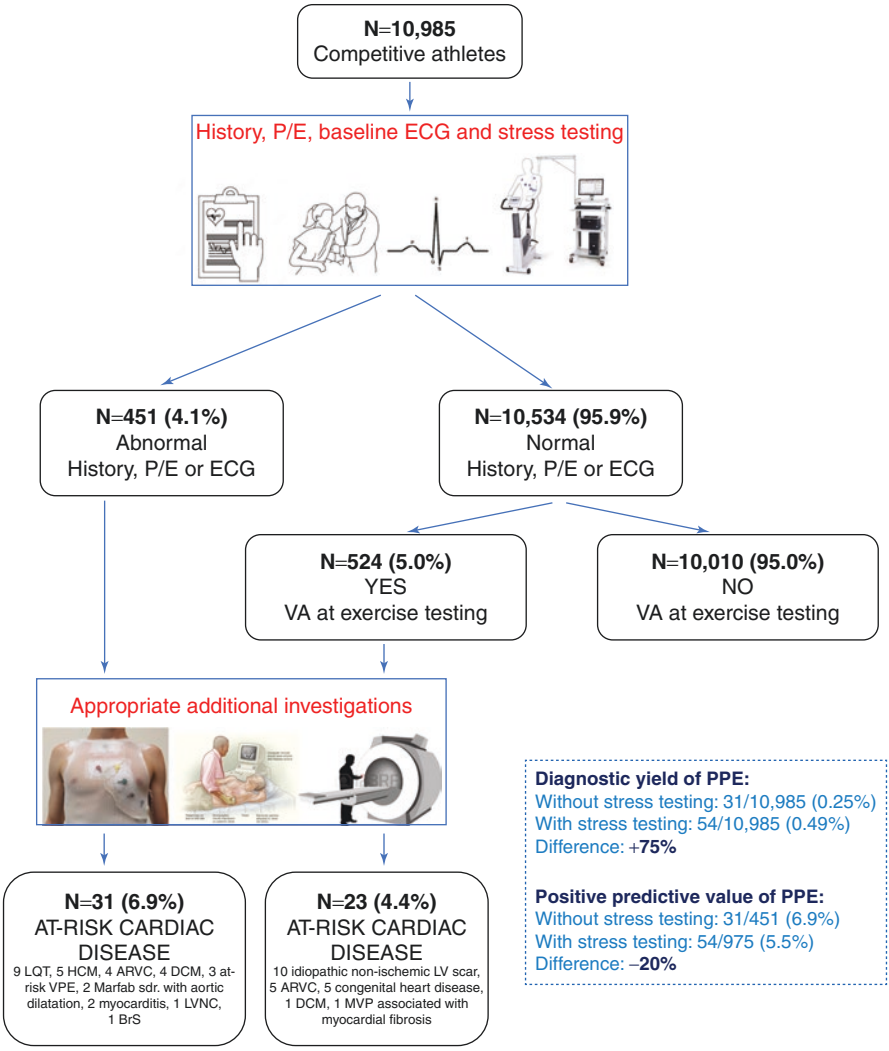

Fig. 8.4 Schematic representation of the study protocol and result. *ARVC* arrhythmogenic cardiomyopathy, *BrS* Brugada syndrome, *DCM* dilated cardiomyopathy, *ECG* electrocardiogram, *HCM* hypertrophic cardiomyopathy, *LQT* long QT syndrome, *LV* left ventricular, *LVNC* LV non-compaction, *MVP* mitral valve prolapse, *P/E* physical examination, *sdr* syndrome, *VA* ventricular arrhythmia, *VPE* ventricular pre-excitation. (Reproduced with permission from [21])

CMR for ventricular arrhythmias, a left ventricular scar was demonstrated in 28 (11%), mostly with a subepicardial/midmyocardial (nonischemic) distribution. Independent predictors of the presence of the scar were the presence of PVBs with RBBB-like pattern or multiple morphologies and recording of exercise-induced

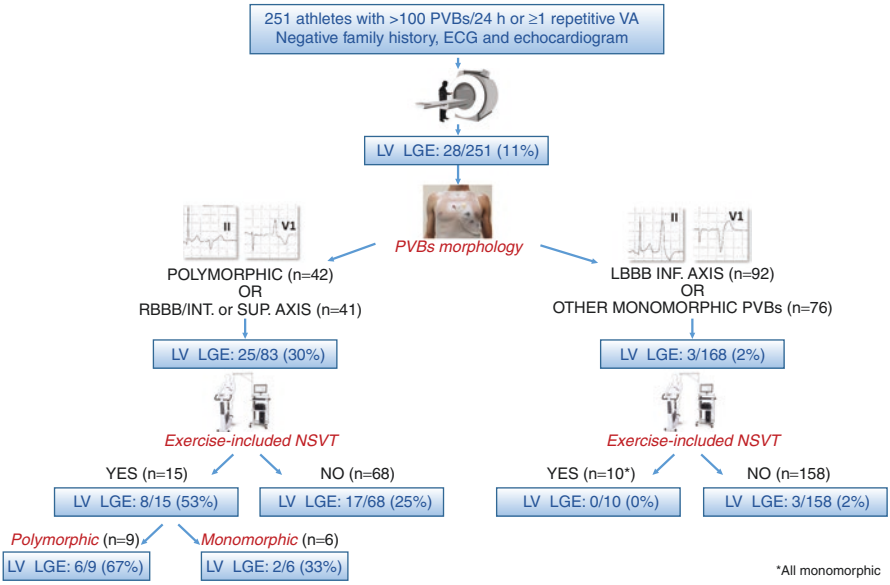

Fig. 8.5 Summary of the main findings of a multicenter study on 251 athletes who underwent cardiac magnetic resonance for apparently idiopathic ventricular arrhythmias. The presence of PVBs with a right-bundle-block/intermediate or superior axis or multiple morphologies, the occurrence of exercise-induced non-sustained ventricular tachycardia (NSVT), and a number of PVBs <3000/24-h on ambulatory ECG were independent predictors of an underlying left ventricular scar. (Reproduced with permission from [22])

non-sustained ventricular tachycardia, while a high number of PVBs (>3300/day) predicted a normal CMR (Fig. 8.5) [22].

The correlation between PVBs and nonischemic left ventricular scar has been reported also in the general population. Muser et al. found late enhancement at CMR in 16% of 518 subjects (44 ± 15 years-old) who underwent the exam for frequent PVBs (>1000/day). Among the predictors of pathological myocardial substrate were polymorphic PVBs and PVBs with non-infundibular morphology. Individuals with pathological CMR findings had a higher incidence of a composite endpoint (SCD, aborted SCD, and sustained ventricular tachycardia) during a median follow-up of 67 months. The incidence of major arrhythmic events was 29% in subjects with late enhancement at CMR, in keeping with previous data regarding the potentially fatal manifestations of left ventricular nonischemic scar. All three patients who suffered SCD died during physical or emotional stress, underscoring once again the precipitating role of sport activity in individuals with PVBs and underlying myocardial disease [23].

To summarize, data emerged in recent years demonstrated that left ventricular nonischemic scar is an important substrate for malignant ventricular arrhythmias

occurring typically during sport activity. The major PVBs characteristics that should raise the suspicion of an underlying scar in athletes with otherwise normal findings are (1) the RBBB-like, wide QRS and superior axis morphology in isolation or associated with other morphologies and (2) the increase in number and complexity of the arrhythmia during exercise.

8.5 Diagnostic Workup of Premature Ventricular Beats in Athletes

The presence of PVBs in the athlete troubles the clinician because some of them are associated with cardiac disorders and SCD during physical activity. For this reason, athletes with PVBs should be investigated with a variety of diagnostic tests aimed to rule out or confirm a possible myocardial disease. Even though the more recent recommendations for the interpretation of the ECG in the athlete suggests performing additional testing in the presence of at least two PVBs at the basal ECG, a single PVB with a non-infundibular morphology must be considered as a red flag [24].

First-line investigations in athletes with PVBs should include history, physical examination, stress ECG test, 12-lead 24-h ECG Holter (recording a training session), and echocardiography [4]. The presence of ECG changes at the basal ECG significantly increases the probability that the ectopic beats are associated with myocardial disorders. The main electrocardiographic abnormalities linked to cardiomyopathies or channelopathies are repolarization abnormalities (T wave inversion and ST segment depression), long QT, short QT, Brugada pattern, conduction disturbances, ventricular pre-excitation, and pathological Q waves [5, 25, 26].

Stress ECG test is a fundamental tool to unmask electrocardiographic abnormalities or arrhythmias that could not be present at the basal ECG. To document possible ischemic changes (ST-T alterations), the effort must be maximal, and a test must be conducted up to the muscular exhaustion reaching more than 85% of the predicted maximal heart rate. Likewise, adrenergic-dependent PVBs might not be evident until a high heart rate is reached, unveiling a latent arrhythmic potential. The echocardiogram has a key role in identifying structural abnormalities, such as valvular defects, cardiomyopathies, congenital disorders, and anomalous origin of the coronary arteries [26, 27].

If one of the abovementioned first-level investigations gives abnormal results, a complete diagnostic approach oriented to the clinical suspect must be followed (i.e., CMR to rule out a possible cardiomyopathy or coronary computed tomography angiogram to exclude ischemic cardiomyopathy).

In the presence of a high index of suspicion for cardiac disease based on the characteristics of the PVBs (morphology, complexity, and relation to exercise), it is indicated to continue the diagnostic workup with a CMR even if the first-line examinations were normal (Table 8.1).

Recent studies demonstrated that considering both PVB morphology and their relation with physical exertion leads to a good specificity for the identification of pathological myocardial substrates [20, 21]. On the contrary, isolated PVBs with infundibular/fascicular morphology that tend to disappear during physical effort can

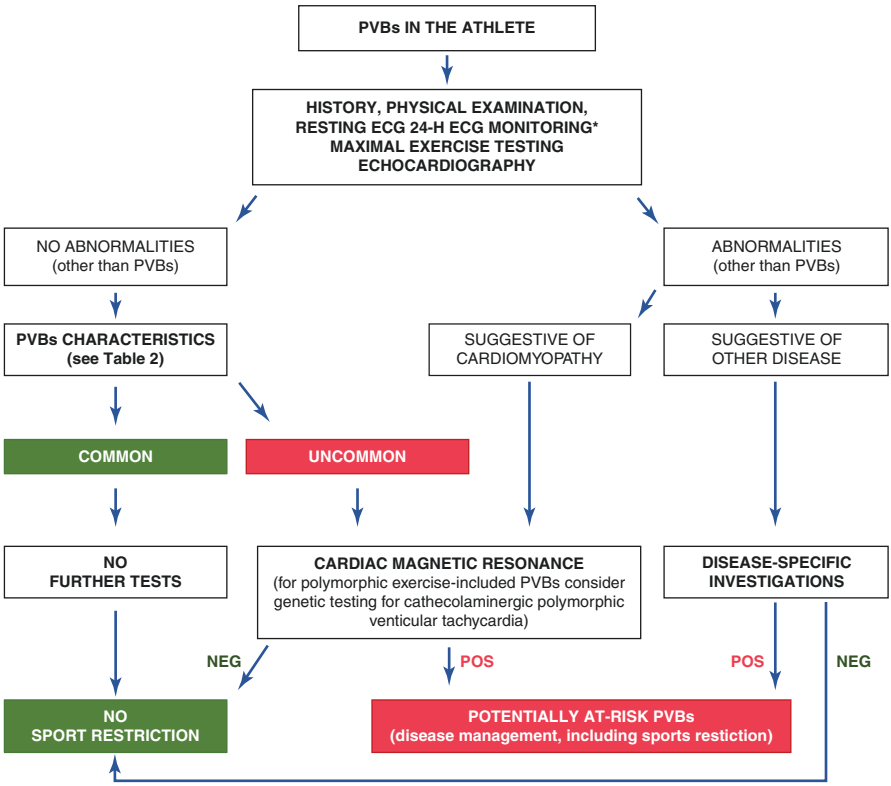

Fig. 8.6 Proposed algorithm for evaluation of athletes with premature ventricular beats. *24-h ECG monitoring should ideally have a 12-lead configuration and include a training session. *NEG* negative, *POS* positive, *PVBs* premature ventricular beats

be considered idiopathic and benign, being compatible with training and competition. Figure 8.6 shows a proposal for the interpretation of PVB in the athlete.

8.6 Conclusions

In the last few years, the advent of CMR contributed to clarifying that some athletes with PVBs, which would have been otherwise considered idiopathic using routine investigations, show hidden cardiac abnormalities such as the left ventricular nonischemic scar. Therefore, in the presence of PVBs with at-risk characteristics (on the basis of morphology, complexity, and relation to effort), it is recommended to complete the diagnostic workup with CMR even with a normal echocardiogram and baseline ECG.

The cause and the prognosis of nonischemic left ventricular scar remain a matter of debate. The association with possibly malignant arrhythmias is now held as a dominant concept, but risk stratification is still puzzling in the absence of robust data, particularly when the scar involves only one or two segments of the left ventricle.

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Fear of Sudden Death During Sport Activity and the Long QT Syndrome

9

Peter J. Schwartz, Silvia Castelletti, and Federica Dagradi

9.1 Foreword

Two sport doctors meet in hell. One asks the other, "Why are you here?" "Because I paid no attention to the QT interval, allowed everyone to compete, and two of my patients with long QT syndrome died suddenly, and you?" "Interesting. I was worried to make such a mistake, and whenever the QT interval seemed long, I was telling them that they could have died any minute and to forget any sport activity. Most of them had no disease, but their lives were ruined." Close by, there was a much older doctor, and the first two recognized him and asked, "You too are here, Professor! Why?" and the reply was "Sorry, guys. This is my entire fault. In my academic cardiology lessons, I never told the students what the long QT syndrome was."

9.2 Introduction

The task of sport physicians is not an easy one. They see a large number of usually young individuals eager to practice sport who are almost always in excellent physical conditions, and in >99% of cases, there isn't a single reason to worry about their engagement in competitive sports. Still, hidden in this forest of healthy teenagers, there is always the possibility of someone with an arrhythmogenic disorder and who could become at risk of life-threatening arrhythmias during a stressful sport activity. It takes attention, concentration, and knowledge to identify the odd subject who

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might really be at risk. Thus, this is a situation in which errors may happen. The trouble is that these errors, when they occur, are paid by those who should have been protected by the doctors.

One of the cardiac conditions which often causes problems to sport physicians, either because its diagnosis is missed or because it is made without reason, is the congenital long QT syndrome (LQTS). In this chapter, we briefly summarize its key features, which should already be known to most sport physicians, and will then focus on practical aspects such as when to suspect LQTS in an asymptomatic individual, how to measure the QT interval, what to do if the suspicion is real, and how to decide on the sticky issue of the sport eligibility certificate, given also the frequent parental pressure. Finally, we will present a novel and unexpected finding that truly represents a potential diagnostic trap for sport physicians. One objective of this chapter is to show the sport doctors that they are not left alone in making decisions when facing a long QT interval and that there is the possibility of sharing responsibility.

9.3 Key Features of LQTS

LQTS is a genetic disorder characterized by QT interval prolongation on the ECG, by typical repolarization abnormalities, and by susceptibility to life-threatening arrhythmias [1, 2]. It is uncommon but not rare having a prevalence of 1 in 2000 live births [3]. The arrhythmias, usually Torsades de Pointes ventricular tachycardia, commonly occur during conditions associated with increased sympathetic activity such as psychological or physical stress but sometimes occur at rest or nighttime. The symptoms consist of syncope, cardiac arrest, and sudden death. The arrhythmias are effectively prevented by β-blockers and by left cardiac sympathetic denervation [1, 4–6], while in the most serious cases an implantable cardioverter-defibrillator (ICD) is used [1].

It is caused by mutations on 17 genes, of which 3 are responsible for almost 85–90% of cases [2]. This has changed the terminology as we now refer to LQT1 (caused by mutations affecting the I_{Ks} current), to LQT2 (caused by mutations affecting the I_{Kr} current), and to LQT3 (caused by mutations affecting the I_{Na} current). Relevant to a discussion about sport activity is the fact that the conditions, or triggers, associated with the life-threatening arrhythmias are largely gene-specific [7]. Indeed (Fig. 9.1), 90% of the lethal events for LQT1 patients occur during either exercise or emotions [7]. This is due to the fact that mutations on the *KCNQ1* gene cause an impairment of the I_{Ks} current whose activation is necessary to shorten action potential duration (and thereby the QT interval) whenever heart rate increases and the RR intervals decrease. If this shortening does not occur, ventricular fibrillation is likely to follow. By contrast, as shown by the arrows in Fig. 9.1, LQT2 and LQT3 patients are at low risk during exercise because they have a normal I_{Ks} current. The first practical implication here would be that concerns for exercise and sport activity should be largely, but not exclusively, focused on LQT1 patients. The second unavoidable practical implication is that to make a sound decision requires knowing the genotype of the patient, which confirms that genetics have fully entered the area of correct clinical management and can no longer be regarded as a fancy toy for researchers [8].

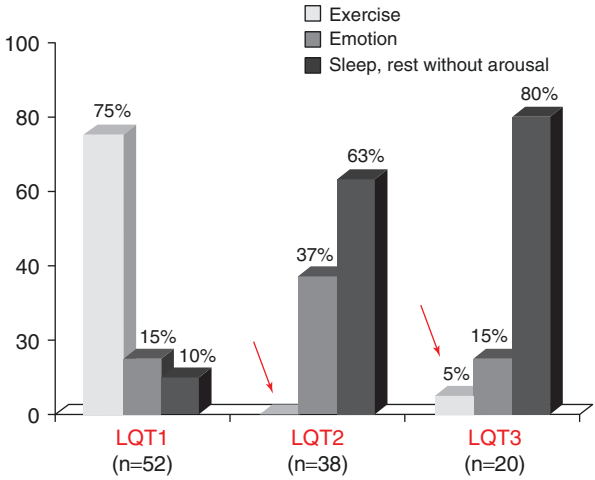

Fig. 9.1 Lethal cardiac events according to triggers and genotype. Numbers in parenthesis are triggers, not patients. (Modified from [7], with permission)

Having made a few general statements about LQTS, complemented by the necessary references for the interested reader, we can now move to discuss some of the problems facing sport physicians and some of the errors that need to be avoided, beginning with the correct measurement of the QT interval.

9.4 Problems and Errors

The accurate measurement of the QT interval requires attention and a bit of time. It was indeed to save time that the so-called "tangent method" was proposed on the basis that it facilitates the identification of the point where the descending limb of the T wave crosses the baseline. At first glance, this is true; however, as with most oversimplifications, this approach has an inherent fundamental error. Indeed, this method becomes actually misleading whenever the descending limb of the T wave has a slow component, which happens often when there is an impairment of I_{Ks} and $I_{Kr,}$ as it is the rule in 90% of cases of LQTS. When these ionic currents are impaired, as in LQT1 and in LQT2, there is a delayed return of the T wave to baseline despite a fast initial downslope. The tangent method can, therefore, lead to an underestimation of the QT interval and should not be used when there is a suspicion of LQTS [2] (Fig. 9.2).

9.5 What Should Not Happen

Unfortunately, it is not infrequent that subjects who should have been promptly recognized at least as "likely affected by LQTS" were superficially considered as normal by the sport physicians who were supposed to examine them. Here, we present just two out of the many similar cases. They should serve as a reminder that these unjustifiable

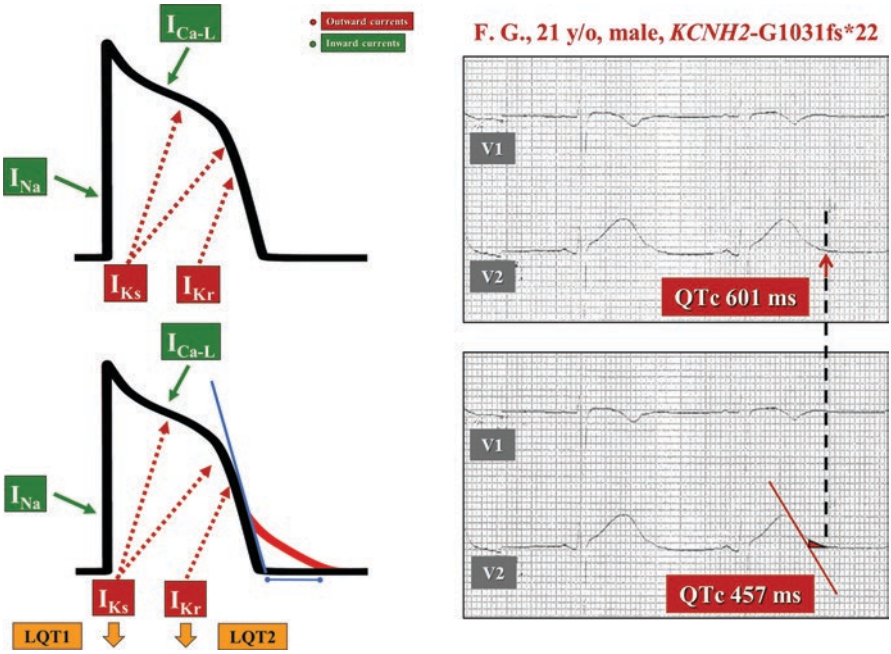

Fig. 9.2 Example of the underestimation of QTc using the "tangent method." On the left, a ventricular action potential. On the right, the basal ECG of a 21-year-old boy affected by LQT2. The ECG trace on the bottom shows the QTc calculation using the tangent method. The red triangle corresponds to the delayed return of the T wave. This is caused by the partial loss of function of I_{Ks} and/or I_{Kr} (bottom of the left side of the figure), and it can be missed by the tangent method: including it (upper part of the right side of the figure) allows the correct QTc calculation

medical errors could have serious consequences for the life of the subjects and for the sport doctors as well, because they often carry medico-legal consequences.

After an earthquake during the night, a 13-year-old boy was found by the father irresponsive, struggling to breathe, with his eyes wide open. He woke up after a few minutes and was carried to the hospital. The electrocardiogram showed a markedly prolonged QT interval (QTc around 550 ms) which prompted the diagnosis of LQTS and the initiation of therapy with β-blockers. Genetic testing revealed a deletion on *KCNH2*. The patient was a soccer player who had been playing since age 5 and who had always undergone pre-participation screening including electrocardiograms considered normal for his age (Fig. 9.3). In this case, luckily, no cardiac events occurred until the diagnosis was made and correct therapy was instituted.

The second example is that of a 6-year-old girl who had undergone an electrocardiogram for pre-participation screening reported normal, despite a QTc greater than 550 ms and of deeply inverted T waves in the precordial leads (Fig. 9.4). Several months later, she started to have syncopal episodes with seizures. While in the hospital, several episodes of Torsades de Pointes ventricular tachycardia occurred, and she was implanted with an ICD. Genetic testing revealed a *de novo* mutation on *KCNH2*. The ICD was prematurely implanted before even starting β-blocker

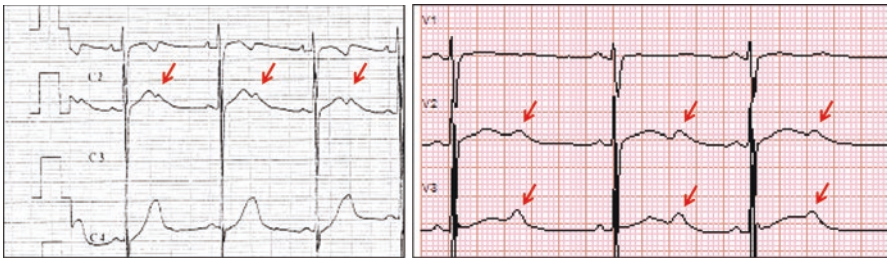

Fig. 9.3 On the left, the basal ECG performed during pre-participation screening in 2014 (QTc 542 ms). On the right, the trace of the 12-lead Holter monitoring performed at our center in 2016 (QTc 560 ms). The arrows indicate notched T waves

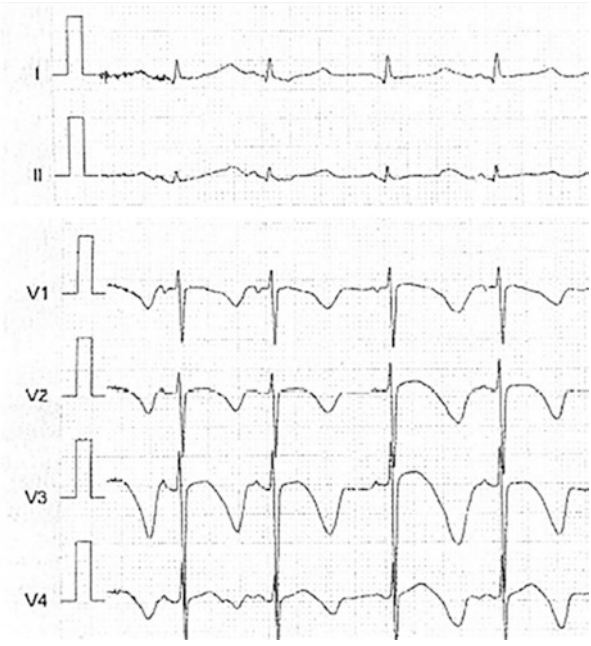

Fig. 9.4 Basal ECG performed during pre-participation screening. QTc in lead I: 536 ms, QTc in lead V3: 582 ms. Deeply inverted T waves are present in lead V1–V4. This tracing was regarded as normal by the sport doctor

therapy, and this little girl already had adverse events caused by the ICD, as it happens in 25% of LQTS patients [9]. Several years have elapsed since β-blockers initiation, and not a single arrhythmic episode has occurred. If the sport doctor had at least requested a second opinion, the diagnosis of LQT2 would have been made, β-blockers would have been initiated, and in all likelihood, she would have remained asymptomatic and certainly would have not received an ICD. These can be the consequences of a superficial assessment by a sport physician.

These examples should be a stark reminder that errors can be made, and indeed, they are made too often. Even if it is understandable that when a sport physician examines the ECG of a teenager, he/she does not expect to encounter a carrier of a potentially lethal genetic disorder, it is exactly his/her responsibility to be aware

that—with a prevalence of 1 case in 2000 births [3]—this would not be an exceptional event and that, therefore, this possibility should be always kept in mind.

9.6 A Dangerous Trap

Until the mid-1990s, the rules for the diagnosis of LQTS were rather simple: if your QTc was close to 500 ms and you had a bizarre T wave, you were affected, period. Those were the halcyon days. Then came the genetic revolution, and we had to confront the phenotype-positive genotype-negative individuals but, as it was accepted that in close to 20% of the patients, a disease-causing mutation could not yet be found, we made peace with ourselves and made the diagnosis on the basis of the ECG pattern. However, the headaches were not over.

At one point, we began to observe, with surprise, that some young athletes with marked QT prolongation and diagnosed by us as affected by LQTS normalized their ECGs after detraining. We were puzzled by this unexpected change, which was questioning the validity of our diagnosis, and we started looking intentionally at what was happening with detraining after the diagnosis of LQTS. We were well positioned for an in-depth study because, being a leading referral center in Italy for sport physicians who suspect the possibility of LQTS in the large numbers of youth who apply for the mandatory sport eligibility certificate, we receive a constant flow of young athletes with abnormal repolarization. What happened next was a lesson in serendipity.

Indeed, there was no study design, no hypothesis to be tested, nothing besides our curiosity and our clinical sense that something was amiss. This unorthodox approach bore fruit and provided meaningful results [10].

The study involved 310 consecutive subjects referred to us because the sport physicians suspected a possible LQTS. They were all actively practicing sports with many hours of intensive weekly training. Of them, 111 had a normal ECG or different cardiac diseases or were lost to follow-up and exited the study; they were a sort of false alarms, but they also indicated that the referring sport doctors were good enough not to want to miss a possible case of LQTS, and this is always a merit. Of the remaining 199, all with either clear QTc prolongation and/or typical repolarization abnormalities, in 121 we diagnosed LQTS on the basis of the combination of ECG abnormalities with positive genotyping, and their average QTc was 482 ± 35 ms. Genetic testing was negative in 78 subjects, but 45 were nonetheless diagnosed as affected by LQTS based on unequivocal ECG abnormalities, and their QTc was 472 ± 33 ms. The other 33, entirely asymptomatic and with a negative family history, following detraining showed an unexpected and practically complete normalization of the ECG abnormalities, as their QTc shortened from 492 ± 37 to 423 ± 25 ms, $p < 0.001$, and their mean Schwartz score went from 3.0 to 0.06 (Fig. 9.5). We regarded them as not affected by congenital LQTS, and we refer to them as "cases." Most significant was the fact that, among this group, those who resumed a similarly heavy physical training showed reappearance of the repolarization abnormalities (Fig. 9.6).

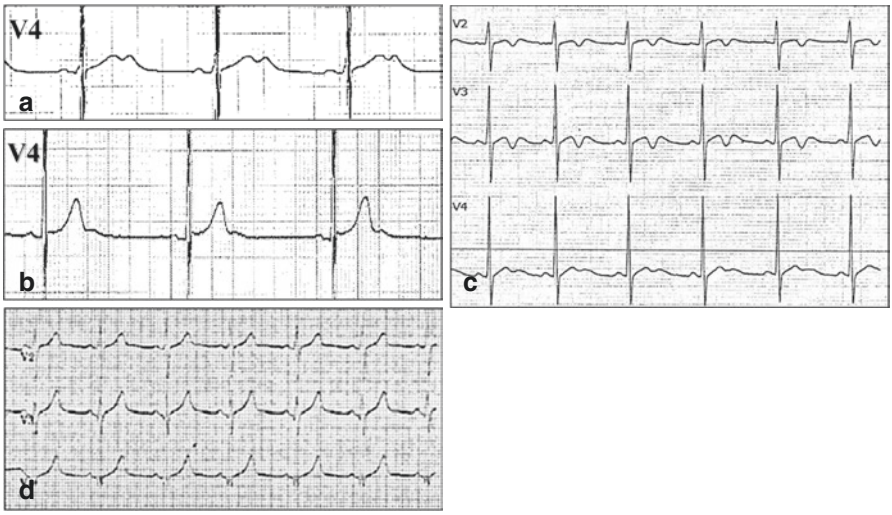

Fig. 9.5 QTc and repolarization abnormalities at pre-participation screening. Left, male, 17-year-old, Rugby player at a competitive level. (**a**) Our center—QTc 495 ms. Detraining was recommended; (**b**) Our center—after 4-month detraining, 380 ms. Right, male, 15-year-old, swimming at a competitive level. (**c**) At pre-participation screening, QTc 536 ms in V3, HR 83 bpm. (**d**) Our center—after 7-month detraining, ECG with normal morphology, QTc 447 ms in V4, HR 76 bpm. (From [10], with permission)

The mechanism underlying the reversible QT prolongation caused by physical training is not yet known. As it happens in a small minority of the youngsters who practice sports, this major QTc prolongation is not a normal physiologic phenomenon and probably represents an abnormal response to physical training possibly due to a genetic predisposition. The obvious analogy is with drug-induced LQTS (di-LQTS) [11, 12], and these repolarization abnormalities induced by exercise training might represent another form of acquired LQTS similar to that of di-LQTS. We call it "exercise-induced LQTS" (Exi-LQTS). Our current hypothesis is that the hearts of certain individuals have a predisposition (genetic or otherwise) to react to augmented mechanical stretch with an activation of stretch-activated channels [13] leading to an increased intracellular release of Ca^{2+}, which prolongs repolarization and largely explain their abnormal ECGs. Following detraining and the attendant progressive decrease in mechanical stretch, the action potential duration of the cardiac myocytes would progressively shorten with a return toward normal ventricular repolarization.

Thus, we have provided novel evidence that, among the athletes presenting with an LQTS phenotype but who are genotype-negative, almost 40% normalize their ECG after detraining and are not affected by LQTS. This finding *per se* has an important impact on their quality of life. They should be considered cases of an acquired and reversible form of LQTS, induced by intense exercise training. These results should change our current diagnostic procedures in all genotype-negative subjects leading to a reassessment of the initial diagnosis after an adequate period

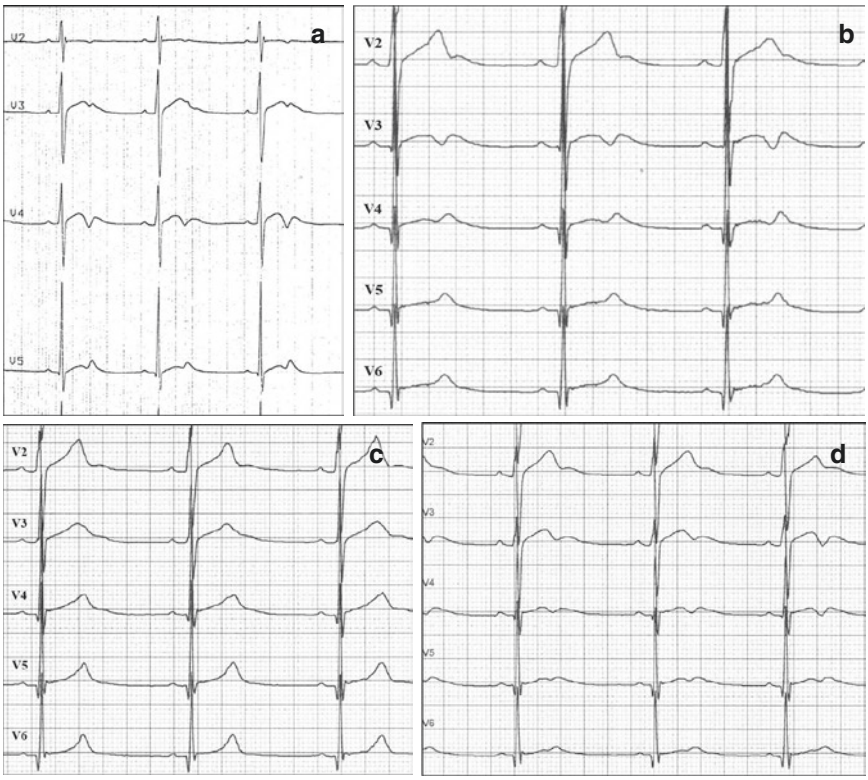

Fig. 9.6 Male, 14-year-old, water polo player at a competitive level. (**a**) At sport visit, QTc 511 ms in V4, HR 50 bpm. (**b**) Our center—still on training, nighttime Holter recording showing repolarization abnormalities (QTc 547 ms in V4, HR 47 bpm). (**c**) After 4-month detraining, the nighttime Holter recording at the same HR shows QTc normalization and normal repolarization (QTc 440 ms in V4, HR 48). (**d**) The patient returned to competitive sport, and after 4 months of retraining, the repolarization abnormalities reappear extending to V6 with a QTc of 550 ms in V4, HR 53 bpm. (From [10], with permission)

of detraining. This will allow to recognize those athletes who, despite their presenting ECGs, do not have the congenital LQTS and who should be managed as if they had drug-induced LQTS. Thus, they could be allowed to practice sport but at an intensity that does not trigger reappearance of repolarization abnormalities, and they should avoid taking I_{Kr} blocking drugs.

9.7 Our Approach and Our Recommendations

Our views have been expressed a few times [14, 15], and we stand by them. However, several points deserve to be mentioned or reinforced.

A critical one concerns the "law of the land." There are countries with specific laws, and in some, Italy for example, in the presence of a diagnosis of LQTS a sport doctor cannot sign the sport eligibility certificate, unless the patient has a very low-risk profile (asymptomatic, without family history, with QTc <480 ms). In other countries, there is even more leeway. A distinction is made between competitive sports and leisure activities, but often, "defensive medicine" prevails, and sport physicians prefer to stay on the safe side and do not give the green light. This upsets the asymptomatic youngster who feels perfectly well and wants to practice sports with his/her friends, and it troubles the family, leading to significant tensions. Often, the diagnosis is not 100% certain, and sport physicians can come under a lot of pressure. This is when the support, as consultants, of a group with unquestionable expertise in LQTS can be very helpful.

Conceptually, it is important to keep in mind that exercise training potentiates vagal tone and vagal reflexes. We have provided multiple evidence that powerful vagal reflexes associate with increased risk of arrhythmias among LQTS patients [16, 17]. This implies that while "play" should be permitted and perhaps encouraged because of its psychological effects, actual intense training should be discouraged.

Often, sport doctors stop the ECG recording for the exercise stress test after just 1 or 2 min of recovery: they should continue for 4 min because changes at this point have proven useful for the diagnosis of LQTS [18] and are part of the diagnostic score [1].

There is also the often difficult issue of which type of sport is more or less likely to be dangerous for an LQTS patient. Team sports are the worst because group pressure forces the subject to perform at his/her maximum limit, whereas individual sports, including tennis, allow the individual choice of how much effort to invest in a single shot. Cold increases sympathetic activity, which means that intense exercise when it is cold could be more dangerous.

Our final message has to do with preventing potentially lethal errors. We have witnessed tragedies simply because a sport physician, not quite sure whether he/she was dealing with a case of LQTS or with a normal kid, decided nonetheless to ignore any doubt and regard it as normal. In this regard, it seems appropriate to literally quote what we have written in a recent past [1]: *To our colleagues who may see LQTS patients only occasionally, we say that, when in doubt, the most appropriate path is to consult with experts in the field: it is never wrong in medicine to admit "limited knowledge or experience" in a specific case, provided that this is followed by the appropriate next steps. Here, we wish to share with them that we, despite the many years spent dealing with LQTS and our daily encounters with these families, not infrequently send out emails to each other and three to four of our most respected colleagues throughout the world and, often within hours, receive extremely important advice that either supports or modifies our plans for these patients. If we do it, everyone else can.*

The bottom line, and our parting statement, is that our group is always available to discuss with sport physicians their cases, if so requested, because we do believe in sharing knowledge and expertise and also because this has been a lifetime policy [19].

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Short QT Syndrome

10

Chiara Scrocco, Fiorenzo Gaita, and Carla Giustetto

10.1 Background

The short QT syndrome (SQTS) is a rare cardiac ion channel disease predisposing to ventricular arrhythmias (VAs) and sudden cardiac death (SCD) in the young [1]. The signature feature of SQTS is the presence of a constantly short QT interval at ECG in the absence of structural cardiac abnormalities. First described in 2000 [2], SQTS was recognised as a potentially inheritable condition predisposing to SCD in 2003 [3], and the demonstration of the first genetic mutation soon followed [4]. In the last 20 years, approximately 200 affected subjects have been reported in the literature worldwide, with few case series published so far [5–8]. Data from the Euro Short Registry published in 2006 [5] and 2011 [6] helped in outlining the diagnostic criteria, clinical manifestations and therapeutic strategies for SQTS, which are summarised in the current consensus documents and guidelines on the management of inherited primary arrhythmia syndromes and the prevention of SCD [1, 9].

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10.2 ECG Diagnosis of Short QT Syndrome and Differential Diagnosis

10.2.1 QT and QTc Interval

The cornerstone of SQTS diagnosis is the documentation of a short QT interval on the surface ECG; however, as the QT interval duration is affected by fluctuations in the heart rate and autonomic tone, a single ECG is not sufficient to confirm the diagnosis. Also, hormonal factors linked to age, race and sex, electrolyte abnormalities and medications are known to affect the duration of repolarisation and therefore the QT interval. To adjust for the heart rate dependence of the QT interval, the absolute value is corrected using specific mathematical formulas, most commonly Bazett's formula ($QTcB = QT/\sqrt{RR}$) [10]. However, its performance at extreme heart rates is suboptimal and may lead to under- or overestimation of the QT interval. Alternatively, Fridericia's [11], Framingham's [12], Hodges' [13] and Rautaharju's [14] formulas can be used. Epidemiological studies showed that the corrected QT interval has a normal distribution in the general population [15–22], and the lower limit of normality can be set at 2 standard deviations from the mean values, therefore at 360 ms in men and 370 ms in women without an excess of mortality in the subjects with short QT [23]. In a cohort of 18,825 healthy individuals aged 14–35 years, of which 8939 (47%) athletes, the prevalence and medium-term prognosis of an isolated short QT interval were evaluated [22]. Twenty-six subjects displayed a QT interval ≤320 ms (0.1%), 44 ≤330 ms (0.2%) and 1478 <380 ms (7.9%). In the athlete population, the QTc showed a normal distribution, and only 15 subjects showed a QTc ≤320 ms (0.17%). While athletes showed slightly shorter QT intervals than non-athletes, the association between athletic status and QTc interval ≤320 ms was not statistically significant. The follow-up data available for a small proportion of subjects with very short QTc values (8/26, 31%) showed again no adverse events over a 5.3 ± 1.2-year period.

These epidemiological studies show that in the general population, including athletes, the finding of short QT-QTc intervals on isolated resting ECG is not associated with an increased risk of SCD. It is also important to point out the need to exclude acquired causes of QT interval shortening, including not only electrolyte imbalance (hyperkalaemia or hypercalcemia), carnitine deficiency, drugs such as digitalis and ATP-sensitive K+ channel activators but also acetylcholine and catecholamines. Hyperthermia and acidosis, both of which can occur in athletes, are important causes of reversible QT interval shortening. The last *ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* suggested a cut-off value of QTc ≤340 ms for the diagnosis of SQTS (it was ≤330 ms in the 2013 *HRS/EHRA/APHRS Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes* [1], with values up to 360 ms still acceptable in subjects with confirmed pathogenic mutations, family history of SQTS or of SD at a young age and personal history of VAs with no other explanation [9]. A diagnostic score system defining the probability of having SQTS (considered as

"high", "intermediate" and "low") based on the evaluation of clinical, familial, ECG and genetic data has been proposed [24]. The ECG variables included in this score are QTc value ≤370 ms (1 point), ≤350 ms (2 points), ≤330 ms (3 points) and J-Tpeak ≤120 ms. The analysed population comprised all SQTS cases reported in the literature until May 2010; however, the score has not been validated in an independent population of SQTS patients, and it is not currently recommended for the diagnosis of SQTS.

The evaluation of several ECGs and of the QT/RR relationship are, in our opinion, a fundamental step in the evaluation of subjects with suspected SQTS.

10.2.2 QT/HR Relationship

As the range of QT intervals in individuals with SQTS and healthy individuals from the general population overlaps, a single QTc value cannot distinguish all affected subjects. Due to the malignant potential of the disease, it is of paramount importance to distinguish between borderline cases and pre-symptomatic individuals potentially at risk of SCD. Therefore, the first step in clarifying the diagnosis among subjects with a suspected short QT interval is to perform repeated resting ECG and stress and 24 h ambulatory ECGs (preferably 12 leads) to evaluate the QT duration at different heart rates.

The analysis of the QT and QTc behaviour during exercise test in healthy individuals from the general population displays a linear relationship between absolute QT and HR [25]; this finding holds true in SQTS patients, who however show lower adaptation of the QT interval at increasing HR. In a study including 21 SQTS patients, the mean variation of the absolute QT interval from rest to peak effort was significantly lower when compared with 20 healthy controls (48 + 14 ms vs 120 + 20 ms, $p < 0.0001$) as well as the mean β-slope of the linear QT/HR relationship (−0.53 ± 0.15 vs −1.29 ± 0.30, $p < 0.0001$) [26] (Fig. 10.1).

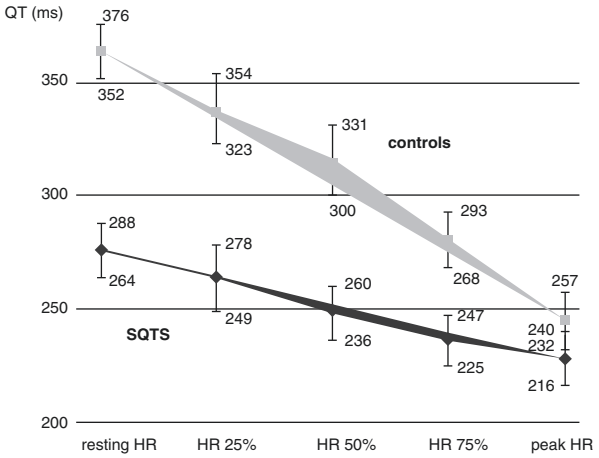


Fig. 10.1 QT/ HR relationship in SQTS patients (dark grey) vs healthy controls (light grey) during exercise tolerance test, from resting to peak HR. See text for details

Twenty-four-hour Holter monitoring allows to evaluate the QT interval at different heart rates during the day and specific activities. The main advantage of 24 h ECG monitoring is the possibility to explore the QT duration at lower heart rates (i.e. during night time) and the presence of spontaneous silent arrhythmias.

We performed an analysis on 17 asymptomatic subjects with high probability (G1) and 30 with low-intermediate probability (G2) of SQTS based on the Gollob score [24] from the Euro Short Registry undergoing 24 h ambulatory ECG monitoring (*unpublished data*). For each subject, extracts from the 24 h ECG recording were obtained at several heart rate intervals from 40 to 120 bpm (40–50 bpm, 51–60 bpm, 61–70 bpm, 71–80 bpm, 81–90 bpm, 91–100 bpm, 101–120 bpm) and the QT interval measured. In G1, the average HR at which the QTc values rose above 360 ms was 84 ± 18 bpm vs 67 ± 10 bpm in G2 ($p < 0.05$). Moreover, in G1, only nine subjects showed QTc values in the normal range in at least one of the heart rate intervals explored, whereas in eight subjects QTc were constantly below the normal limits, for HR up to 120 bpm (Fig. 10.2). Therefore, the simple evaluation of the QTc at 24 h ECG can identify subjects with short QT only at lower heart rates and help overcome QTc value misinterpretations due to brady- or tachycardia. This may prove especially helpful in the athlete population which show low resting HR [27].

10.2.3 Other ECG Features

10.2.3.1 T Wave Morphology and J-Tpeak Interval

SQTS type 1 cases are characterised by narrow, tall, peaked and symmetrical T waves, with no clear ST segment. This characteristic is more evident in affected males. In SQT2 and in most non-genotyped patients, the T wave is still tall and symmetrical, despite being less sharp. In SQT3, the T wave may show an asymmetrical pattern with a rapid terminal phase. The J-T peak interval, the interval between the

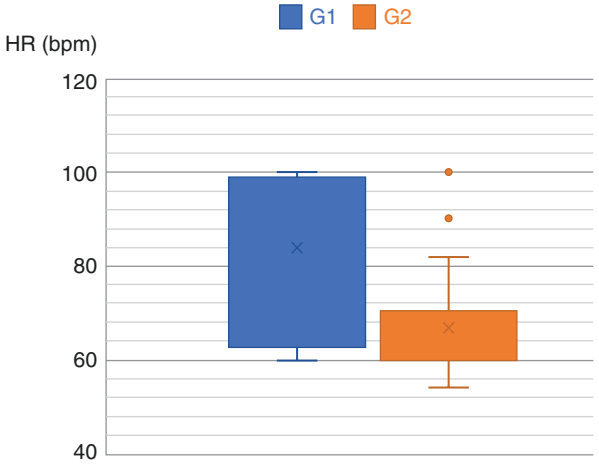


Fig. 10.2 Range of HR at which the QTc values fall in the normal range (≥360 ms) in high-probability SQTS subjects (G1) vs low- probability SQTS subjects (G2). See text for explanations

end of the QRS complex (the J point) and the peak of the T wave (T peak) have been found to be shorter in SQTS patients compared to subjects with short or normal QTc values from the general population, with values comprised between 80 and 120 ms [28].

10.2.3.2 PQ Segment Depression

In a study on 74 SQTS patients, PQ depression (PQD), defined as >0.05 mV (0.5 mm) depression from the isoelectric line, has been observed in 81% of cases as compared to 24% of healthy controls [29]. These findings have not been replicated in independent cohorts.

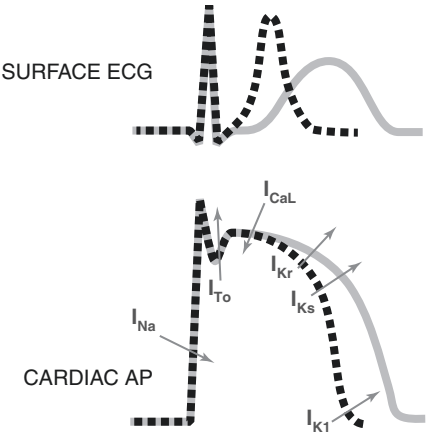
10.2.3.3 Early Repolarisation Pattern

The early repolarisation pattern (ERP) is defined as a J point notch or slur, the J wave, of at least ≥0.1 mV in ≥2 contiguous leads (excluding leads V1 − V3), on the downslope of a prominent R wave with or without ST-segment elevation [30]. The ERP is a common ECG finding, being present in 1–13% of the general population, and is more frequent in males and in some ethnicities [1]. ERP is present in up to 45% of Caucasian athletes and 63–91% of athletes of African-Caribbean descent [27]. Whilst traditionally considered a benign phenomenon, in recent years, ERP has been associated with unexplained cardiac arrest due to VF [31], and it is believed to confer a greater risk of arrhythmias in both structural and non-structural cardiac conditions, including primary inherited arrhythmias [32]. ERP has been suggested to be highly prevalent in SQTS and associated with adverse outcome [33]. However, these findings have not been validated in external cohorts.

10.3 Genetics and Molecular Basis

SQTS is an autosomal dominant disorder, and mutations in three genes encoding the pore-forming subunit of the rapidly activating-delayed rectifier potassium channel (KCNH2-SQTS1), the KvLQT1 subunit of the slowly activating-delayed rectifier potassium channel (KCNQ1-SQT2) and the inwardly rectifying potassium channel (KCNJ2-SQTS3) have been associated with the disease [4, 34, 35]. The resultant effect of these mutations is a gain-of-function with increased channel activity and acceleration of repolarisation. Loss-of-function mutations in the L-type calcium channel subunit genes CACNA1C and CACNB2 are responsible for an overlapping phenotype of SQTS and Brugada pattern ECG [36], and another mutation in the CACNA2D1 gene has been associated with short QT intervals [37]. More recently, loss-of-function mutations in the cardiac sodium channel voltage-gated encoding gene SCN5A [38] and in the cardiac chloride-bicarbonate exchanger AE3 [39] have been associated with short QTc intervals; however, no conclusive data exist for the causative effect of these variants (Fig. 10.3).

In the largest case series published in the literature, the yield of genetic testing proved to be low (~20% of index cases). Currently, comprehensive or SQT1–3 targeted SQTS genetic testing may be considered for any patient with strong clinical



Genetic defects associated with SQTS		
GENE, protein	Current	Effect
KCNH2, Kv 11.1	I_{Kr}	↑
KCNQ1, KvLQT1	I_{Ks}	↑
KCNJ3, Kir2.1	I_{K1}	↑
CACNA1C, Cav1.2	I_{CaL}	↓
CACNB2, Cavβ2b	I_{CaL}	↓
CACNA2D1, Cavα2δ-1	I_{CaL}	↓

Fig. 10.3 Schematic representation of the surface ECG and ventricular cardiac action potential (AP) with the ionic currents involved in its phases. Solid light grey images represent the physiological AP and normal surface ECG beat, while black, dotted lines represent the cardiac AP and ECG in SQTS

suspicion for SQTS based on clinical history, family history and electrocardiographic phenotype, and mutation-specific genetic testing is recommended for family members following the identification of the SQTS-causative mutation in index cases [40]. No precise genotype–phenotype correlation data are available to inform the individual risk based on the genetic background. Moreover, variable expressivity has been suggested [7], and a possible role of genetic modifiers has been proposed [41]. Although there is some evidence that SQTS1 subjects show a greater response to medical therapy with hydroquinidine [6], at present, therapeutic strategies are not influenced by genetic findings. Similarly, there are no data on the impact of genetic findings on the risk of arrhythmic events during competitive sport in SQTS.

10.4 Clinical Manifestations and Mechanisms of Arrhythmias

SQTS affects predominantly males (above 75% of cases), with a mean age at the observation of 26 years [6]. At least half and up to two-thirds of affected subjects have symptoms at observation, of which cardiac arrest is the most frequent, in up to 32%. Syncope of presumed arrhythmic origin is the first clinical presentation in less than 20% of cases (13–16%), and AF at a young age has been documented in 11% of subjects in the Euro Short series [6]. Unexplained SCD can be observed in individuals of all ages, especially in newborns and young adults aged between 20 and 40 years. It has been estimated that the probability of experiencing CA between birth and 40 years of age is between 40 and 50% [7].

With regard to the circumstances in which cardiac arrest or SCD occur, there are no clear triggers for arrhythmias, and in the vast majority of cases (83%), cardiac

arrest occurs during sleep or at rest. The role of the autonomic nervous system in arrhythmogenesis in SQTS is largely unknown; however, as the impaired QT/RR relationship is more pronounced at slower heart rates, VAs are more likely to occur at slower resting HR, after abrupt RR cycle length variations. Although the first description of SQTS was based on extremely short QT and QTc values (≤280 and ≤300 ms, respectively) associated with life-threatening arrhythmias [3], the QTc duration is not a recognised prognostic marker. Experimental studies using cellular and animal models [42–45] allowed to elucidate the potential arrhythmogenic mechanisms for SQTS due to potassium-channel hyperactivation (secondary to impaired inactivation, faster activation, slowed deactivation or constitutive opening), leading to shortened cardiac AP, atrial and ventricular effective refractory periods (ERP) (Fig. 10.3). Regional differences in the channel distribution would determine inhomogeneous AP duration between the different cardiac layers (being shorter in the epicardium), determining increased transmural dispersion of repolarisation (TDR) and refractoriness, ultimately leading to both atrial and ventricular re-entrant arrhythmias. The increased TDR is reflected in the augmented Tpeak–Tend at surface ECG [42]. In vivo EP studies on SQTS patients and transgenic rabbits with the N588K-KCNH2 mutation showed not only short atrial and ventricular ERP but also greater additional shortening after premature extrastimuli [3, 44, 46]. This facilitates circus-type or spiral wave phase 2 re-entrant arrhythmias (polymorphic VT and VF) triggered by spontaneous short-coupled PVCs or couplets [6, 47, 48] (Fig. 10.4) and leading to syncope or SCD. It has been reported, however, that also long-coupled PVCs can initiate VF in SQTS [7].

10.5 Management of SQTS Patients

The implantable cardioverter-defibrillator (ICD) represents the treatment of choice for subjects with aborted CA or documented spontaneous sustained VAs, given the high incidence of recurrent events [1, 7, 9]. The intravenous ICD experience in SQTS patients is burdened by a high incidence of complications (inappropriate shocks due to T wave oversensing, lead fractures, infections requiring extraction of the device and psychological distress) with rates up to 51% in adults and 80% in children [8]. Data on the use of subcutaneous ICD are limited [49, 50].

Due to the lack of defined risk stratification tools, primary prevention strategies in asymptomatic subjects from SQTS families are not well codified. In fact, ECG, genetic and instrumental data failed to accurately predict the risk of arrhythmias in this group [6], and individualised clinical decisions are usually adopted. According to Expert Consensus documents, medical treatment with quinidine or sotalol may be considered in asymptomatic subjects with family history of SCD despite the fact that only quinidine has been tested in a considerable proportion of patients and with adequate follow-up data [6, 51], whereas the experience with sotalol is limited and with inconsistent results [41]. Quinidine has also been used successfully for the prevention of VA recurrences in subjects with ICD and previous arrhythmic events and for the prevention of atrial arrhythmias.

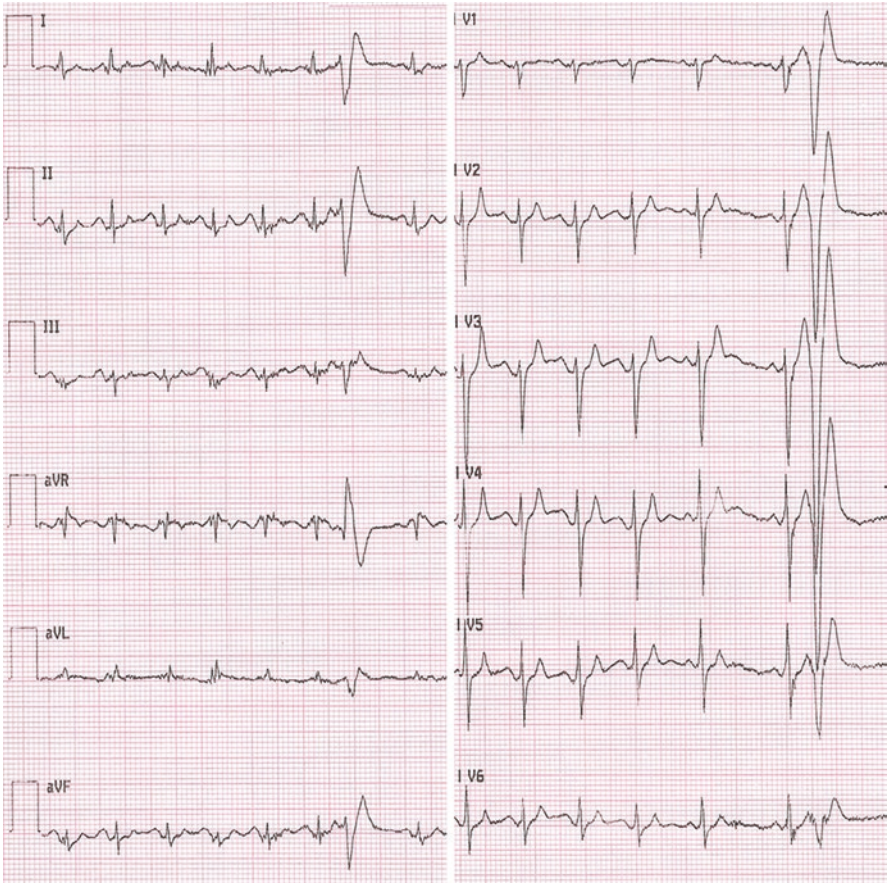


Fig. 10.4 Short-coupled PVC in SQTS Short-coupled PVC (coupling interval 190 ms) during exercise test with R-on-T phenomenon in a 32-year-old female with SQTS1 and N588K-KCNH2 mutation

10.6 Sports Recommendations

In the largest SQTS cohort published, the annual risk of cardiac arrest was approximately 1%, with only a minority of cardiac arrests occurring during emotional stress or physical effort (17%) [6, 7]. SQTS therefore shares similarities with Brugada and early repolarisation syndrome, and it has been suggested that cases of idiopathic VF may represent under recognised forms of SQTS [52]. As no specific triggers for STQS arrhythmic events have been identified, the consequences of strenuous physical activity in SQTS patients are largely unknown. While the importance of screening techniques including resting 12L ECG, 24 h ambulatory ECG and stress ECG, is paramount to identify subjects with abnormally short QT/QTc values [53], the diagnosis of SQTS may be challenging, and a comprehensive evaluation by a heart rhythm specialist with expertise in inherited cardiac conditions is advisable. The

official guidelines for sport eligibility have evolved from a complete ban of competitive sports (except those with low static or dynamic demand) [54] to a permissive approach, also in previously symptomatic athletes, after adequate counselling, initiation of treatment if needed, appropriate precautionary measures (including the acquisition of personal automatic defibrillator) and absence of symptoms for at least 3 months [55]. The last *2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease* [56] do not offer specific recommendations for sport eligibility in SQTS patients.

In conclusion, there is no evidence to date that athletes with isolated short QT intervals should always be considered ineligible for sports participation. Instead, they should undergo a multi-parametric assessment to evaluate their probability of having short QT syndrome. In those with confirmed SQTS diagnosis, careful consideration of individual risk factors (i.e. the presence of symptoms, especially during exercise, documented arrhythmias, family history of SCD, specific genetic mutations, response to medical therapy) should guide a personalised approach to sport eligibility or return to play after an event. This strategy will benefit from the availability of more prospective data from international SQTS registries, also including athletic individuals (Table 10.1).

Table 10.1 Prevalence of short QT interval in the general population

Study (Ref)	Population	QTc value	Subjects with short QT	Unexplained SD/syncope
Gallagher [15]	12,012 Italian occupational records database mean age 29.6 ± 10 years	≤360 ms	60 (0.5%)	0
Anttonen [16]	10,822 Finnish population mean age 44 ± 8.4 years	≤320 ms ≤340 ms ≤360 ms	11 (0.1%) 43 (0.4%) 269 (2.5%)	0 0 0
Moriya [17]	19,153 Japanese longitudinal cohort mean age 40 ± 15.8 years	≤350 ms	2 (0.01%)	0
Kobza [18]	40,917 Swiss conscripts mean age 19.2 ± 1.4 years	≤320 ms	8 (0.02%)	0
Funada [19]	10,984 Japanese hospital-based population mean age 51 ± 21 years	≤300 ≤364 ms	3 (0.03%) 158 (1.43%)	0 0
Miyamoto [20]	105,824 Japanese hospital-based population Mean age 52.6 ± 20.7 years	≤369 ms	427 (0.4%)	1
Guerrier [21]	99,380 ECG database at a single paediatric institution <21 years	≤340 ms	45 (0.05%)	1 (DCM)
Dhutia [22]	18,825 UK subjects undergoing cardiac screening mean age 19 ± 5 years	≤320 ms ≤330 ms	26 (0.1%) 44 (0.2%)	0 0

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Brugada ECG Pattern and Brugada Syndrome

11

Pietro Delise

Brugada syndrome is a possible cause of sudden death.

Brugada syndrome was first described in 1992 by Pedro and Josep Brugada, who reported eight cases of patients with idiopathic cardiac arrest (i.e., without obvious heart disease) who had a particular ECG pattern. This pattern was characterized by J point elevation of 2 or more millimeters, down-sloping ST elevation, and a negative T wave in right precordial leads (BrS ECG pattern) [1] (Fig. 11.1). Their paper created panic in cardiologists and (presumed) patients all over the world. In reality, however, this ECG pattern is not so rare; consequently, the first obvious question was, are all subjects with a BrS ECG pattern at risk of sudden death or only some of them?

In most cases, a BrS ECG pattern is discovered by chance during routine ECG [2]. Only seldom is it found after an arrhythmic syncope (Figs. 11.1b and 11.2a). In some cases, a BrS ECG pattern is discovered, in the absence of symptoms, after the administration of drugs such as 1 C anti-arrhythmic drugs taken for atrial fibrillation.

After the original description of the BrS ECG pattern (subsequently called BrS type 1 ECG), type 2 and type 3 BrS ECG patterns were also described [3] (Fig. 11.1). These two latter patterns were introduced because, in patients with Brugada syndrome, the BrS type 1 ECG may be intermittent and, at different times, types 2 and 3 BrS ECG patterns may be recorded.

In any case, the pattern associated with Brugada syndrome is BrS type 1, while BrS types 2 and 3 are not specific. Nevertheless, in clinical practice, BrS type 2 and type 3 ECG patterns and sometimes also incomplete right bundle branch block are frequently regarded as suspect patterns for Brugada syndrome, which creates considerable confusion.

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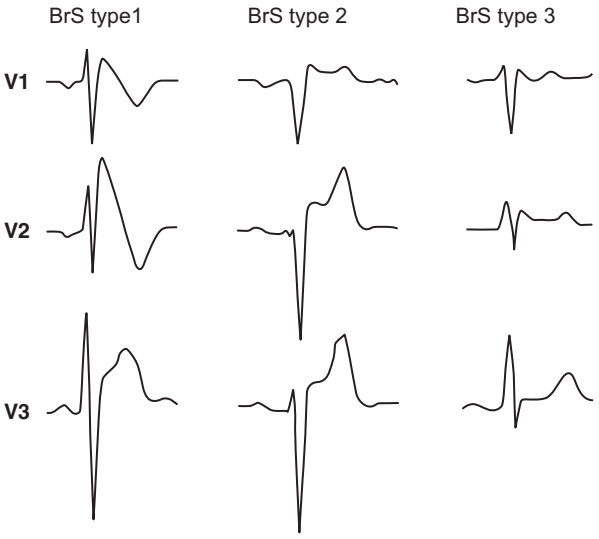

Fig. 11.1 The three BrS ECG types. Type 1 (left) is the typical BrS type ECG described in the original paper by the Brugada brothers [1]. BrS type 2 (middle) and BrS type 3 (right) are aspecific ECG patterns, which can be observed in subjects with intermittent BrS type 1 ECG

Confusion increased after the introduction of drug tests (with ajmaline, flecainide, etc.). Such tests were proposed in subjects with syncope of undetermined origin, in order to disclose a BrS type 1 ECG pattern and thus a concealed Brugada syndrome [4, 5]. Subsequently, these tests were also widely extended to asymptomatic subjects with atypical ECGs, creating an enormous mass of presumed Brugada syndromes in otherwise healthy people [6].

Thus, the concept that a Brugada syndrome cannot be excluded in anybody spread throughout the world; as S. Viskin wrote, "Everybody has a Brugada syndrome until proven otherwise" [7]. It is incredible that this serious problem has arisen from an electrocardiographic signal which, in the vast majority of cases, is not pathological.

11.1 Brugada Type 1 ECG and Prognosis

Most patients with a BrS type 1 ECG have a benign prognosis, particularly those with a drug-induced BrS type 1 ECG [8].

We recently published a cumulative multicenter prospective study of over 1500 patients (mean age 44 ± 14 years) with a BrS type 1 ECG without ICD, who had generally been judged at low risk [9]. During follow-up, subjects with a drug-induced BrS type 1 ECG had a very low incidence of SD (0.06% × year), which was similar to (slightly lower than) that of the general population. By contrast, those with a spontaneous BrS type 1 ECG displayed an incidence of SD of 0.38% per year, which was higher than that of the general population; it was, however, lower than that of patients with hypertrophic cardiomyopathy (HCM), who are considered to be at low risk and in whom the European Society of Cardiology does not recommend ICD implantation [10] (Fig. 11.3).

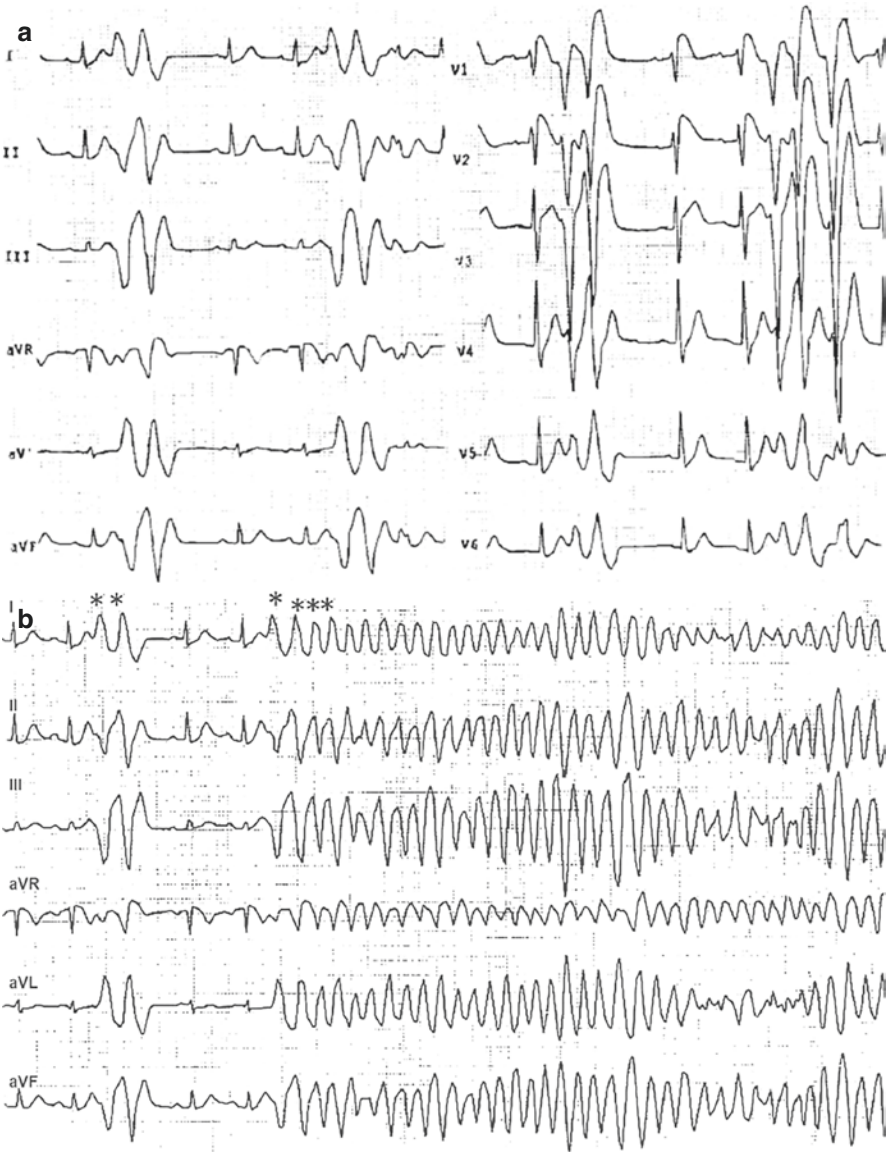

Fig. 11.2 (**a**) Male aged 35 years old, admitted to the emergency room for recurrent syncope. Frequent VPBs in couples and triples can be noted. In sinus beats, a typical BrS type 1 ECG is present in leads V1–V2. (**b**) Same case as in (**a**). Ventricular fibrillation is initiated by very premature VPBs

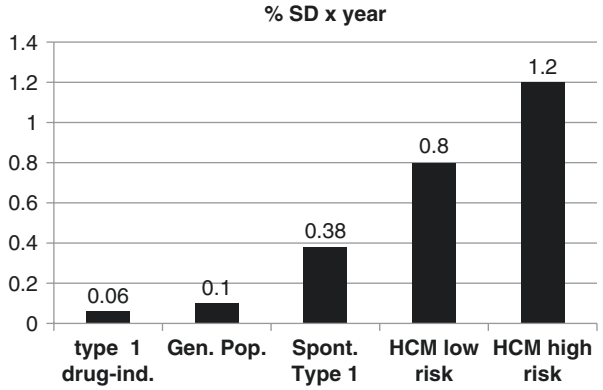

Fig. 11.3 Incidence of sudden death x year in subjects with BrS type 1 pattern without ICD implantation, from Delise P. et al. [9]. The population includes both patients with spontaneous and drug-induced BrS type 1 who were prospectively followed up. The incidence of SD in this population is compared with the incidence in the general population aged >30 years (Gen. Pop) and in HCM patients, who are considered to be at low and high risk, respectively, by the European Society of Cardiology. As can be seen, subjects with drug-induced BrS type 1 had a similar incidence of SD to that of the general population. In contrast, subjects with a spontaneous BrS type 1 had a higher incidence than the general population. However, the incidence was lower than in low-risk HCM patients, in whom the ESC does not suggest ICD implantation

It is therefore evident that a BrS type 1 ECG and Brugada syndrome are not synonymous, in contrast with the suggestions of current European guidelines [11].

11.2 Genetic Basis of Brugada Syndrome

It is currently accepted that Brugada syndrome is determined by defects of genes (such as SCN5A, SCN1B, and SCN1B), leading to a loss of function of the main sodium channel, Nav1.5. However, a defect of these genes is found in no more than 30% of patients with Brugada syndrome.

In addition, in families with SCN5A mutations, the BrS type 1 ECG is present in only 47% of mutation carriers, while 5% of genotype-negative subjects have a BrS type 1 ECG pattern [12].

Finally, similar genetic defects may be found in other diseases, such as Lenegre's disease, sick sinus syndrome, early repolarization syndrome [13, 14]. Moreover, it is interesting that, in families with defects of genes encoding Na+ channels, some patients present with a Brugada type 1 ECG, some present with conduction disturbance and others with both ECG anomalies.

Although it is difficult to reach a conclusion, all these data suggest that SCN5A mutations do not directly cause a BrS type 1 ECG and that other factors (genetic and nongenetic) may play a role in the occurrence of this pattern. In addition, Brugada syndrome has recently been attributed to delayed depolarization of the anterior aspect of the right ventricular outflow tract [15].

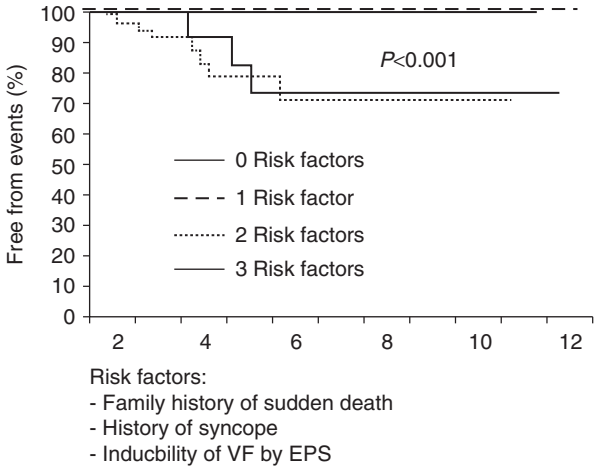

Fig. 11.4 Incidence of cardiac events in subjects with spontaneous BrS type 1 ECG; from Delise P et al. [17]. As can be noted, patients who had no or only one risk factor had no events. In contrast, all patients with events had 2 or more risk factors (among family history of SD, syncope, and/or inducibility of FV by EPS)

11.3 Risk Stratification in Individuals with Brugada Type 1 ECG Pattern

Prospective studies [16–21] have identified a number of risk factors which are useful (singly or in association) in identifying patients with a Brugada syndrome (at risk of malignant arrhythmias) within the great number of subjects with a BrS type 1 ECG: spontaneous BrS type 1 ECG, first-degree AV block, fragmented QRS, syncope of presumed cardiac origin, familial juvenile SD, positive EPS, etc.

When considered individually, however, all these factors have a low positive predictive value and therefore little clinical usefulness in deciding whether to implement therapy. By contrast, several prospective studies conducted in patients without previous cardiac arrest have suggested that the patients at highest risk are those with multiple risk factors [9, 16, 18, 20, 21] (Fig. 11.4).

Interestingly, in our cumulative prospective study of subjects with a BrS type 1 ECG who did not have an ICD [9], the few patients who suffered SD/aSD also had multiple risk factors (i.e., they should have had an ICD implanted).

11.4 Brugada ECG Pattern in Athletes

In athletes, the basal ECG may have characteristics that may be erroneously considered similar to type 1 and 2 BrS patterns (Fig. 11.5). Indeed, trained athletes, especially those of African origin, may physiologically present with right early repolarization (ER) in leads V1–V3. This is characterized by ST elevation in right precordial leads, with a positive (right ER type A) or negative (right ER type B) T wave (Fig. 11.5).

However, in right ER type A, ST elevation is ascending, while in BrS type 2, the ST is horizontal. In addition, in right ER type B, the ST is elevated, and the T wave is negative. However, in right ER type B, ST elevation is ascending, followed by a T wave which is negative only in its second part. In contrast, in BrS type 1 ECG, the J point is elevated, and the ST is descending, followed by a negative T wave.

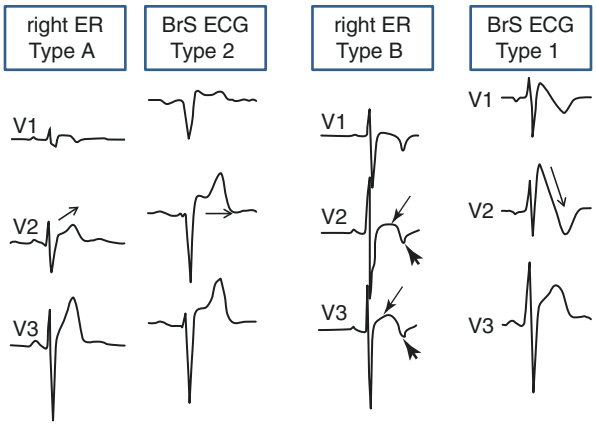

Fig. 11.5 Right early repolarization (ER) in athletes compared with BrS type 1 and type 2 ECG In right ER type A (left), ST elevation is ascending, while in BrS type 2, ST elevation is horizontal. In right ER type B, ST elevation is ascending and is followed by a T wave which is negative in its second part. In contrast, in BrS type 1, the J point is elevated, ST elevation is descending and is followed by a negative T wave

11.5 Brugada Syndrome and Risk of SD Related to Sport Activity

There are no data concerning the possibility that sports activity can trigger SD in subjects with a BrS type 1 ECG. In contrast, as in Brugada syndrome, SD generally occurs during sleep and at rest, and it is unlikely that the increased sympathetic tone may trigger malignant arrhythmias.

It has also been hypothesized that, in athletes, the enhanced vagal tone induced by training may facilitate malignant arrhythmias in Brugada syndrome. However, there are no data to suggest that this is a real possibility. Specifically, there is no proof that, in subjects with a Br type 1 ECG (without confirmed Brugada syndrome), malignant arrhythmias can be facilitated by training.

Finally, no case of cardiac arrest related to Brugada syndrome has ever been described in athletes.

11.6 Sports Eligibility in Subjects with Brugada Syndrome and a BrS Type 1 ECG

In patients with Brugada syndrome (i.e., with proven malignant arrhythmias), it is reasonable to deny eligibility for sport. In patients with suspected Brugada syndrome, i.e., without documented arrhythmias but with multiple risk factors, including syncope, eligibility should also be denied.

In contrast, there is no reason to deny eligibility in subjects with only a spontaneous Br type 1 ECG and no clinical risk factors.

In patients who undergo EPS, if this is negative (−EPS), eligibility should be granted. Indeed, in the presence of a negative EPS (−EPS), the risk of arrhythmias is very low [22].

A problem might arise in patients with positive EPS (+EPS) in the absence of other risk factors. In this case, while the risk increases, the positive predictive value of +EPS alone is low. Therefore, there is no consensus regarding what should be done.

11.7 Drug-Induced Br Type 1 ECG: Indications and Sports Eligibility

In the absence of risk factors, the induction of a Br type 1 ECG pattern by drugs does not increase the risk of SD in comparison with the general population. It therefore follows that there is no reason to extensively prescribe drug test in subjects with type 2 or 3 BrS ECG or in subjects with only minimal ST elevation in right precordial leads. In addition, in subjects with drug-induced type 1 ECG and no risk factors, there is no reason to deny sports eligibility.

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Early Repolarization Syndrome

12

Pietro Delise and Valeria Carinci

Early repolarization (ER) is a common finding in the electrocardiogram (ECG) of young healthy subjects and particularly in athletes [1–3].

ER may be present in right or left leads.

Right ER has been described in the chapter of Brugada syndrome, in which the differential diagnosis between benign right ER and other similar pathologic ECG aspects has been discussed.

In this chapter, we discuss the left ER of healthy athletes and early repolarization syndrome (ERS) [4–6] and, in particular, the differential diagnosis between the two conditions.

12.1 Benign Left ER and ERS Differential Diagnosis

Left ER in healthy athletes has been described many years ago and considered a benign finding [2, 3].

ERS is an ion channel disease, which may be a cause of sudden death in the absence of organic heart disease. ERS may be suspected on the basis of some ECG alterations, which are similar but not equal to benign left ER.

Benign left ER is characterized by slurring or notching of terminal QRS in leads V4–V6 and/ or inferior leads associated with ST elevation in the same leads [5] (Fig. 12.1).

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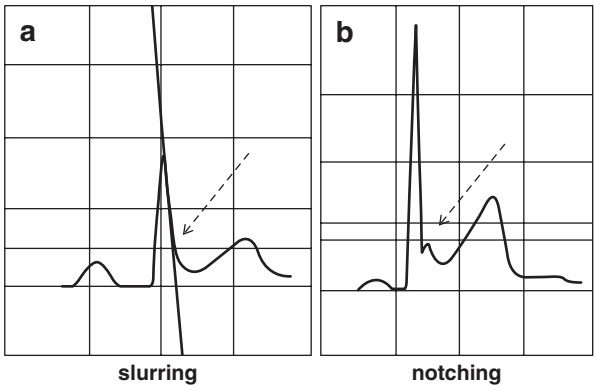

Fig. 12.1 Characteristics of benign early repolarization. The ECG may show slurring (**a**) or notching (**b**) of terminal QRS in leads V4–V6 and/or inferior leads associated with ST elevation in the same leads

In benign ER, during effort terminal, slurring or notching disappears, while the ST segment becomes isoelectric (Fig. 12.2a, b).

The ECG in ERS shows slurring or notching of terminal QRS in inferior or inferolateral leads which, however, is not associated with ST elevation. The latter characteristic is particularly useful to differentiate ERS from benign ER.

12.2 Early Repolarization Syndrome Causes and Complications

ERS is a rare condition. It may be caused by several genetic defects [7, 8] involving Ca2+ (CACNA1C, etc.), K+ (KCNJ8, etc.), or Na+ (SCN5A, etc.) channels.

All these disorders lead to an enhanced sodium inward current limited to epicardial layers of the left ventricle. This provokes an exaggeration of the physiologic notch in phase 1 of the action potential. It follows an electrical gradient between the endocardium and the epicardium creating a positive vector oriented from the endocardium to the epicardium. This phenomenon is localized in the inferior part of the left ventricle [9], and it is recorded as a positive notch at the end of QRS in inferior leads [7, 8] (Figs. 12.3, 12.4a, b, 12.5, and 12.6a, b).

ERS has been recently included in so-called J wave syndromes together with Brugada syndrome [7].

The reason is that the two conditions have a number of similar characteristics.

Both diseases may be due to a genetic defect of SCN5A, leading to a dysfunction of the Na+ channel.

In addition, both diseases generally occur in males, aged between 30 and 50 years; in both, ECG anomalies are dynamic, fever increases ECG alterations, and SD frequently occurs during sleep.

As discussed in Brugada syndrome (see the chapter), also in ERS, the ECG alterations are not specific for the disease. That is, to have an ER with the characteristics of ERS does not automatically mean to have a high risk of SD.

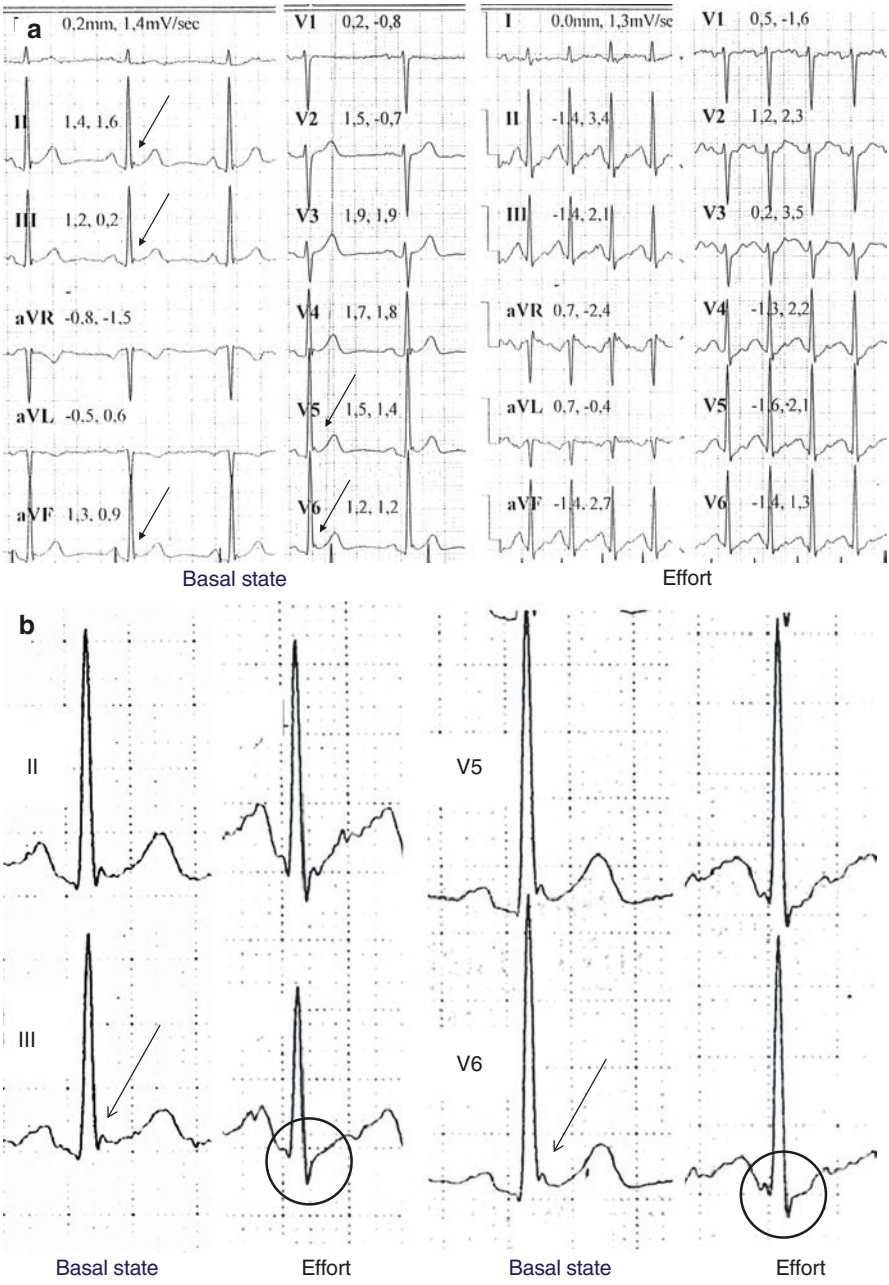

Fig. 12.2 (**a**) 42-year-old male professional cyclist. ECG in the basal state (left) and during effort (right). Arrows indicate early repolarization. Note early repolarization and ST elevation in inferolateral leads in the basal state. During effort, terminal notching disappears, while the ST segment becomes isoelectric. (**b**) Particular of (**a**) reporting inferolateral leads

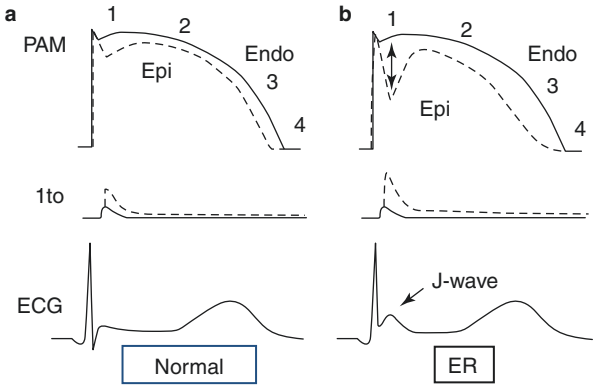

Fig. 12.3 (**a**, **b**) The electrophysiologic mechanism on the basis of ERS is an exaggeration of the physiologic notch in phase 1 of the action potential. It follows an electrical gradient between the endocardium and the epicardium creating a positive vector oriented from the endocardium to the epicardium. As this phenomenon is localized in the inferior part of the left ventricle, it is recorded as a positive notch in inferior leads

In fact, the presence of only an ERS ECG pattern increases the risk of SD from 3.4 × 100.000 to 11 × 100.000 [8].

Similar to Brugada syndrome, subjects at risk are those who have multiple risk factors in addition to the ECG pattern.

A risk score has been suggested [7] to reach the diagnosis which requires at least 5 points for a probable/definite ERS. The variables are family history (2 points), previous cardiac arrest (3 points), syncope of cardiac origin (2 points), ER > 2 mm (2 points), dynamicity of ER (1.5 points), and short-coupled VPBs on ECG (2 points).

For example, a patient with an ERS pattern, with familial history of SD and syncope, reaches 6 points (2 + 2 + 2) which increases to 8 in the presence of short-coupled VPBs on ECG.

In contrast, a subject with only ER > 2 mm (2 points) reaches neither the diagnosis (5 points) nor a suspicion of possible ERS (3–4.5 points).

12.3 ERS ECG Pattern and Risk of SD Related to Sport Activity

Sudden death in ERS generally occurs during the night (cases of Figs. 12.4 and 12.6a).

However, among athletes with ERS resuscitated from cardiac arrest, in 70% of cases, aborted SD occurs during effort and in the remaining on standing after effort [10].

These data suggest that effort and/or training may have a role in the occurrence of malignant arrhythmias in this disease.

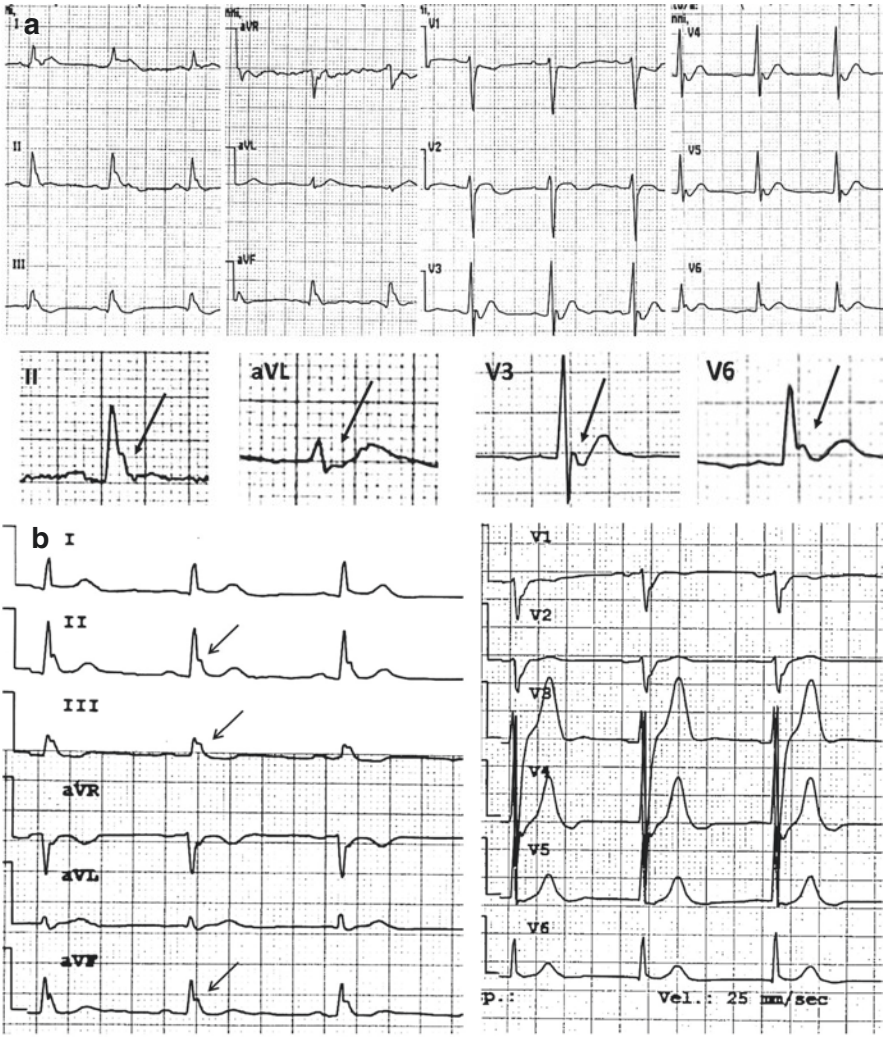

Fig. 12.4 (**a**) Male aged 43 years. Nocturnal cardiac arrest resuscitated by means of cardiac massage and DCS. The ECG recorded in the emergency room soon after the cardiac arrest showed a pattern typical for ERS (arrows). (**b**) Same case as in (**a**). ECG recorded 2 h later in the cardiology department shows a minimal ER in inferior leads

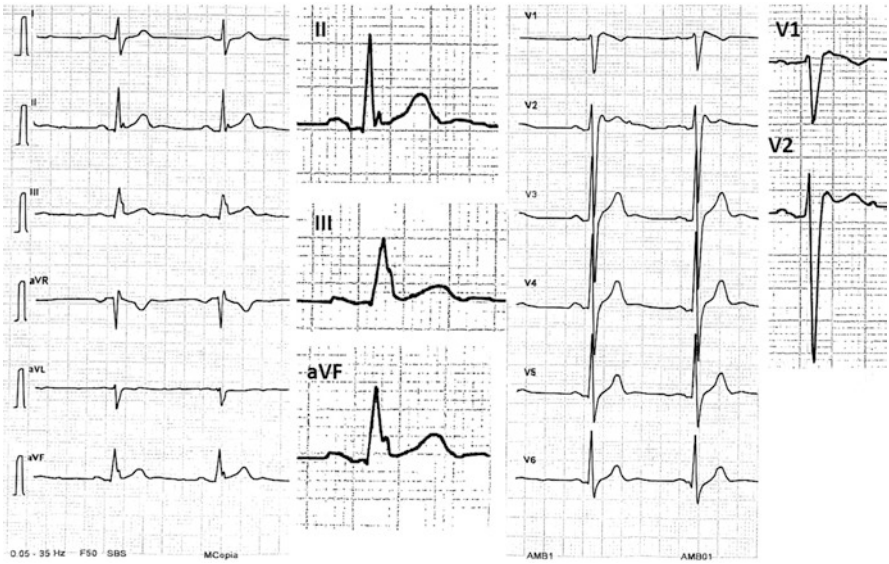

Fig. 12.5 Male aged 40 years. Symptomatic for syncope. The ECG was considered suspected for a Br ECG pattern; he underwent a flecainide test. During drug infusion, ventricular fibrillation occurred. No Brugada type 1 ECG pattern appeared after flecainide. Interestingly, however, in this case, ER was present in the basal state, but was not considered

12.3.1 Sports Eligibility in Subjects with Definite or Suspected ERS

In patients with definite ERS (that is with multiple risk factors in addition to the ECG pattern), eligibility should also be denied.

In subjects with possible ERS (that is with few risk factors, reaching a score between 3 and 4.5), caution should be recommended performing the Holter monitoring, effort test, etc.

In contrast, there is no reason to deny eligibility in subjects without risk factors and only the ECG pattern.

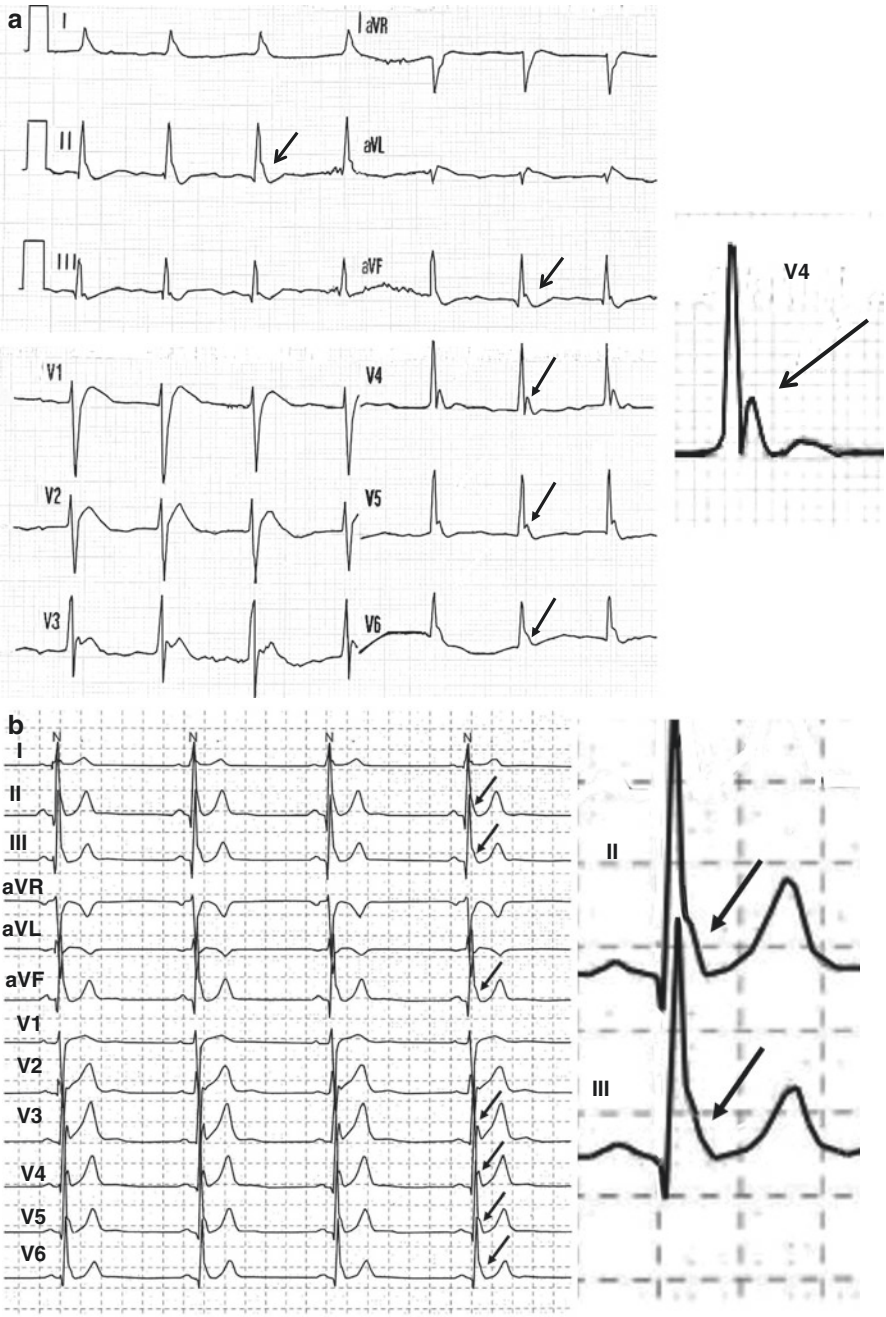

Fig. 12.6 (**a**) Male aged 43 years. Nocturnal cardiac arrest resuscitated by means of DCS. The first ECG recorded in the emergency room showed an ECG pattern suspected for ERS in a VF and V4–V6 (arrows). Being also an ST elevation in V1–V2 ajmaline test was performed which was negative. (**b**) Same case as in (**a**). During follow-up, the ECG continued to show an ECG suggesting ERS

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Catecholaminergic Polymorphic Ventricular Tachycardia

13

Deni Kukavica, Alessandro Trancuccio, Andrea Mazzanti, and Silvia G. Priori

13.1 Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited arrhythmogenic disorder, characterized by a signature pattern of typical, reproducible, catecholamine-induced bidirectional [1], and polymorphic ventricular arrhythmias, in patients with an unremarkable resting electrocardiogram (ECG) and structurally normal heart [2]. Along with other inherited channelopathies, the relevance of CPVT lies in the fact that this condition accounts for a significant portion of unexplained sudden cardiac deaths, especially in young individuals.

CPVT was first described in 1978 as a distinct inherited arrhythmia syndrome by the group led by the French electrophysiologist, Philippe Coumel, who highlighted the main features of the disease and laid the foundations for future studies in the field. In their seminal work, they described a group of four unrelated children, all of whom had suffered syncopal spells, and demonstrated that ventricular arrhythmias were related to catecholamine release [1].

The cause of this lethal disease remained elusive until 2001, when mutations in the cardiac ryanodine receptor (*RYR2*) [3] and in cardiac calsequestrin (*CASQ2*) [4]

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were found to be responsible for the autosomal dominant and recessive forms of CPVT, respectively. Over the last two decades, the genetic background of CPVT has been expanded, with the identification of mutations on other genes, all involved in the maintenance of intracellular calcium homeostasis.

This chapter provides an overview of the current knowledge on CPVT, focusing on epidemiology, genetic background, pathophysiology and arrhythmogenic mechanisms, clinical manifestations and diagnosis, and principles of management.

13.2 Epidemiology

CPVT is a rare disease, with an estimated prevalence of 1:10,000, without sex prevalence [5]. In the absence of accurate epidemiological data, some studies have suggested that the frequency in the general population could be underestimated and that, despite its low prevalence, CPVT accounts for up to 15% of unexplained cardiac arrest cases, especially in young individuals [6].

The age at clinical presentation is between 8 and 10 years, with up to 80% of patients experiencing arrhythmic symptoms by the age of 40 years [7]. In a subset of patients (10–20%), the first manifestation of the disease is cardiac arrest [8]. When left untreated, CPVT is highly malignant, with an estimated mortality rate of 50% before the age of 20 [9].

13.3 Genetic Background

CPVT is recognized as a monogenic disorder, and mutations in seven genes involved in the release of calcium from the sarcoplasmic reticulum (SR) have been identified in connection with the condition (Table 13.1).

Table 13.1 The genetic background of CPVT

Name	Gene	Cytogenetic location	Protein	Transmission	Percentage of patients
CPVT-1	*RYR2*	1q42-q4	Cardiac ryanodine receptor	Autosomal dominant	70%
CPVT-2	*CASQ2*	1q21	Cardiac calsequestrin	Autosomal recessive[a]	5%
CPVT-3	*TECRL*	7p14-p22	Trans-2,3-enoyl-CoA reductase-like protein	Autosomal recessive	<1%
CPVT-4	*CALM1*	14q32.11	Calmodulin-1	Autosomal dominant	<1%
CPVT-5	*TRDN*	6q22.31	Cardiac triadin	Autosomal recessive	2%
CPVT-6	*CALM3*	19q13.32	Calmodulin-3	Autosomal dominant	<1%
Not classified	*CALM2*	2p21	Calmodulin-2	Autosomal dominant	<1%

[a]AD inheritance has been proven for some *CASQ2* variants [10]

13.3.1 Cardiac Ryanodine Receptor (RYR2)

In 2001, we described that mutations in the cardiac ryanodine receptor (*RYR2*) gene, located on the long arm of chromosome 1 (1q42-q43), are the cause of autosomal dominant CPVT (CPVT-1) [3]. *RYR2* gene encodes for the cardiac ryanodine receptor, a large tetrameric calcium-releasing protein located in the membrane of the junctional SR which plays a pivotal role in electromechanical coupling. Gain-of-function *RYR2* mutations are the most common cause of CPVT, accounting for 70% of cases.

13.3.2 Cardiac Calsequestrin (CASQ2)

Shortly after the discovery of *RYR2* as a CPVT gene, mutations in the cardiac calsequestrin gene (*CASQ2*), located on the short arm of chromosome 1 (1p13.1), were identified as responsible for the autosomal recessive form of CPVT (CPVT-2) [4]. Novel works have also identified specific *CASQ2* mutations (e.g., p.Lys180Arg [11]) as autosomal dominant causes of CPVT [10]. Calsequestrin is a calcium-buffering protein situated within the junctional sarcoplasmic reticulum that controls the amount of calcium released from the sarcoplasmic reticulum [12, 13]. Additionally, it modulates the RYR2 channel, inhibiting its opening at low calcium levels, creating a calcium refractory period during which calcium cannot be released again [14]. Currently, it is estimated that *CASQ2* accounts for 5% of CPVT cases.

13.4 Other Genes Associated with CPVT

Five more genes have been associated with catecholamine-mediated VA, but mutations in these genes cause a clinical condition with an intermediate phenotype of CPVT and long QT syndrome. Hitherto, it remains unclear whether these novel genes represent distinct arrhythmia syndromes or merely unusual variants of CPVT.

13.4.1 Triadin (TRDN)

Autosomal recessive mutations in cardiac triadin (*TRDN*), located on the long arm of chromosome 6 (6q22.31), are thought to be responsible for 1–2% of CPVT cases [15]. Triadin is a scaffolding protein which anchors calsequestrin to the ryanodine receptor near the junctional sarcoplasmic reticulum, important for the maintenance of the ultrastructure of the terminal cisternae of the sarcoplasmic reticulum.

13.4.2 Calmodulin (CALM)

Dominant mutations in three calmodulin genes (*CALM1*, *CALM2*, and *CALM3*), located on the long arm of chromosome 14 (14q32.11), the short arm of chromosome 2 (2p21), and the long arm of chromosome 19 (19q13.32), respectively, have been

associated in rare instances (<1%) to CPVT [16–18]. All *CALM* genes generate an identical protein, which plays a major role in binding the calcium in the cytosol and also interacts with RYR2, modulating the probability of its diastolic opening.

13.4.3 Trans-2,3-Enoyl-CoA Reductase-Like (TECRL)

Recently, whole-exome sequencing studies identified mutations in trans-2,3-enoyl-CoA reductase-like gene (*TECRL*), found on the long arm of chromosome 4 (4q13), as a recessive cause of CPVT in patients with overlapping clinical features of CPVT and long QT syndrome [19]. *TECRL* encodes a highly evolutionarily conserved endoplasmic reticulum protein expressed preferentially in the heart, which is thought to play a role in fatty acid and lipid metabolism.

13.5 Pathophysiology

13.5.1 Excitation-Contraction Coupling and Calcium-Induced Calcium Release (CICR)

Excitation-contraction coupling is the mechanism by which the depolarization of the membrane results in the initiation of cardiac contraction [20], and its perturbations are the key to CPVT [21]. During the plateau phase of the action potential, calcium enters through the L-type Ca^{2+} channel (LTCC) at the level of T-tubules and triggers the opening of the cardiac ryanodine receptor. Opening of the ryanodine receptor results in a release of significantly larger quantities of calcium from the sarcoplasmic reticulum, in a process known as *calcium-induced calcium release* (CICR). Subsequently, the increased intracellular calcium interacts with cardiac myofilaments to initiate the process of muscle contraction. During diastole, when the contraction is terminated, calcium has to be removed from the cytosol—either back into the sarcoplasmic reticulum, outside of the cell, or into the mitochondria. This task is accomplished by the SERCA pump, which pumps calcium into the sarcoplasmic reticulum against the concentration gradient in an ATP-dependent process; by the sodium-calcium exchanger (NCX), which extrudes one calcium ions out of the cell in exchange for three sodium ions; and, finally, by a lesser extent, through the cell membrane calcium ATPase (PMCA) and the mitochondrial Ca2+ uniport system (MCU).

13.6 Molecular Pathophysiology

13.6.1 RYR2 Mutations

It is interesting to note how the same gain-of-function effect results from over 170 distinct RYR2 mutations, which have been identified and which span the

entire length of the protein [22]. In the following section, we will illustrate how an *RYR2* mutation may cause a gain-of-function effect via the three mechanisms proposed.

The first mechanism postulates that *RYR2* mutations impair the interaction of RYR2 with its regulatory peptides, such as Calstabin2 (also known as FKBP12.6). The regulatory peptides are important for the stabilization of the channel in its closed state during diastole [23]. The reduced Calstabin2-RYR2 interaction, a result of some *RYR2* mutations, increases the probability of untimely RYR2 opening, resulting in diastolic calcium leak from the sarcoplasmic reticulum [23].

It is not only the interaction with other proteins that may be affected as a result of an RYR2 mutation: the interaction between different domains of RYR2 itself may be altered as well [24, 25]. It is well-established that the interaction between the N-terminal domain and the central domain of RYR2 is crucial for the stabilization of the closed conformation of the channel ("*zipping*") [24]. Certain mutations, located in the central domain (e.g., p.Arg2474Ser), disrupt the interaction between the N-terminal domain and the central domain, weaken the closed conformation of the channel ("*unzipping*"), and result in diastolic calcium leak [25].

Lastly, the third mechanism, called "store overload-induced calcium release" (SOICR), hypothesizes that *RYR2* mutations lower the threshold of luminal calcium required for RYR2 activation (i.e., SOICR threshold) [26, 27]. The increased sensitivity of mutant RYR2 to calcium within the sarcoplasmic reticulum is then further amplified during beta-adrenergic stimulation via protein kinase A (PKA) [28, 29] and Ca2+/calmodulin-dependent serine-threonine protein kinase II (CaMKII)-mediated phosphorylation of *RYR2* [30].

13.6.2 CASQ2 Mutations

As illustrated earlier, CASQ2 plays an important function in the modulation of calcium in the sarcoplasmic reticulum: it buffers sarcoplasmic reticulum calcium and interacts with RYR2 modulating its opening at low calcium levels.

In the majority of cases, the inheritance is autosomal recessive, and mutations cause a reduced or defective synthesis of calsequestrin protein. This results in the perturbation of the normal calcium buffering and RYR2 modulation, likely in varying proportions. The reduction of the buffering capacity of *CASQ2* results in the prolongation of the time interval during which the sarcoplasmic reticulum calcium levels are sufficiently high to reactivate the RYR2 channels [31]. On the other hand, the mutated *CASQ2* alters the interaction of the protein with RYR2, resulting in the impairment of the calcium refractory period [32].

In the recently described dominant *CASQ2*-dependent CPVT, it has been suggested that some mutations [11] may fail to undergo correct polymerization and therefore exert a dominant-negative effect, rather than simple haploinsufficiency [33, 34].

The end result of the aforementioned mechanisms is that RYR2 reactivates during diastole, allowing for diastolic calcium leak [35], just like in *RYR2* mutations.

13.6.3 TRDN Mutations

Triadin mutations are thought to result in decreased levels of the protein, as they may render the protein unstable and lead to enhanced mutant protein degradation [15]. Loss of triadin, as the result of homozygous mutations in *TRDN* gene, results in profound ultrastructural anomalies of the terminal cisternae of the sarcoplasmic reticulum and a reduction of the number of proteins relevant for calcium homeostasis (i.e., RYR2, CASQ2, junctin) [36]. The final outcome of these structural abnormalities is increased calcium current flowing across the LTCC due to impairment of the calcium-dependent inactivation of the said channel, resulting in the prolongation of the cardiac action potential and calcium overload [36].

13.7 Arrhythmogenic Mechanisms

The onset of delayed afterdepolarizations (DADs) and triggered activity (TA) is the converging end point of both *RYR2* and *CASQ2* mutations and is a result of the profound alterations of calcium homeostasis (Fig. 13.1) [21].

CPVT-causing mutations that alter the calcium homeostasis provide the necessary substrate, but in isolation are not sufficient for the occurrence of delayed afterdepolarizations. Beta-adrenergic stimulation, which phosphorylates simultaneously RYR2, increasing its open probability, and SERCA, resulting in increased sarcoplasmic reticulum calcium content, provides the necessary second hit for the diastolic calcium leakage (Fig. 13.1) [21]. Diastolic calcium leakage, in turn, triggers the inappropriate activation of the sodium-calcium exchanger (NCX). Activation of the sodium-calcium exchanger is electrogenic, causing the appearance of delayed afterdepolarizations (Fig. 13.1), which have been demonstrated both in vitro [37] and in silico [38] to be the arrhythmogenic mechanism in CPVT. Importantly, a sufficient number of myocytes need to synchronously develop a delayed afterdepolarization on the same beat [39] in order for the delayed afterdepolarization to cause triggered activity (Fig. 13.1).

Triggered activity will manifest initially as the appearance of premature ventricular complexes (PVCs), organizing into the bigeminal rhythm. Studies in experimental animals (i.e., *RYR2*$^{R4496C/+}$ knock-in mouse) allowed to identify that the typical arrhythmia of CPVT, the bidirectional VT, is the result of an alternating firing of two foci, located in the distal His-Purkinje network of the two ventricles [40] (Fig. 13.1). Importantly, selective ablation of the right ventricular Purkinje fibers results in the substitution of bidirectional VT with a monomorphic VT originating from the left ventricle [40]. In silico studies confirmed these findings, demonstrating that the bidirectional VT is the manifestation of the bigeminal rhythm of two arrhythmic foci, which reciprocally activate [41]. Additionally, the appearance of a third arrhythmic focus seems to be responsible for the transition from bidirectional VT to polymorphic VT [41].

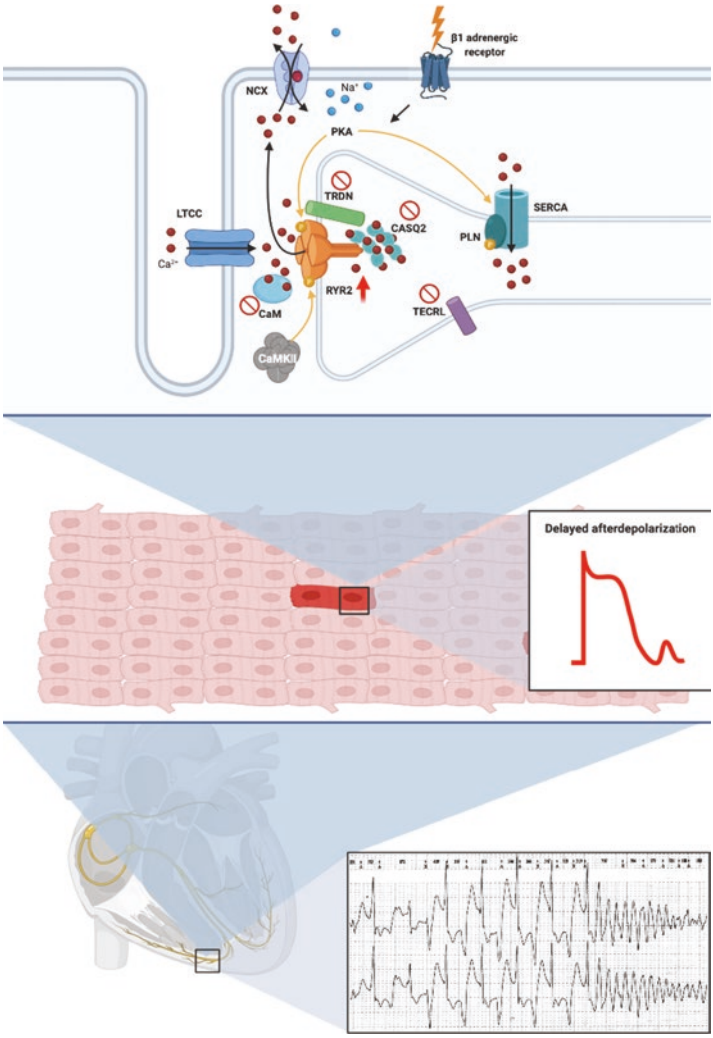

Fig. 13.1 Pathophysiology of catecholaminergic polymorphic ventricular tachycardia. In the presence of CPVT-causing mutations, calcium homeostasis is perturbed. Ryanodine receptor 2 (*RYR2*) mutations or calsequestrin (*CASQ2*) mutations result in diastolic calcium leak from the ryanodine receptor, which is amplified during sympathetic stimulation. This calcium leak causes cytosolic calcium overload, which activates the sodium-calcium exchanger (NCX), which extrudes one calcium ion in exchange for three sodium ions, generating a new inward current. The result of these cellular processes is the appearance of delayed afterdepolarizations (DADs): if a sufficient number of cells spontaneously develop delayed afterdepolarizations during the same beat, triggered activity may occur. DAD-mediated triggered activity represents the key arrhythmogenic mechanism of *RYR2*- and *CASQ2*-related CPVT, while in novel forms of CPVT, caused by *TRDN*, *TECRL,* and *CALM1-3* mutations, other mechanisms may play an important role. Typical arrhythmia of CPVT, bidirectional ventricular tachycardia, is thought to be the electrocardiographic manifestation of the DAD-mediated triggered activity causing a bigeminal rhythm in two alternating foci located in the distal His-Purkinje fibers of the respective ventricles. Although bidirectional ventricular tachycardia is typically stable and regresses with the cessation of catecholamine stimulation, exercise continuation may lead to its degeneration into ventricular fibrillation

At odds with the RYR2- and CASQ2-related CPVT, the arrhythmogenic mechanisms of novel forms of CPVT may appear to be more heterogeneous. Although some specific mutations (e.g., p.Ala103Val on *CALM3* [18]) have been shown to cause delayed afterdepolarization, the prolongation of the QT interval has led to the hypothesis that early depolarizations may be a contributing factor.

13.8 Clinical Manifestations and Diagnosis

The cardinal clinical manifestations of CPVT are exercise- or emotion-induced syncope or cardiac arrest [1], starting from early childhood, with an average age of 8 ± 4 at the first syncope [9]. Owing to the rarity of the disease and its peculiar features (i.e., appearance of arrhythmias only during catecholamine stimulation), multiple syncopal episodes are frequently misattributed to neurological disorders and treated as such, resulting in a long diagnostic delay (2.6 years) [42]. In a non-negligible proportion of patients, unfortunately, a cardiac arrest is the first manifestation of CPVT.

According to the current guidelines [2], the diagnosis of CPVT is made upon the documentation of exercise- or emotion-induced polymorphic VT or bidirectional VT (Fig. 13.2) (i.e., 3 or more beats of ventricular origin with heart rate >100 bpm characterized by a beat-to-beat alternating QRS axis), in the presence of a normal resting electrocardiogram (ECG) and no structural cardiac abnormalities. It is important to highlight that isolated premature ventricular complexes or couplets, in the absence of symptoms, are not sufficient for the diagnosis of CPVT, but should prompt an extensive clinical investigation.

Exercise stress test is the gold standard for the diagnosis of CPVT. Typically, isolated PVCs appear when the heart rate increases above an individual-specific threshold, which in the absence of therapy is fairly reproducible. The ventricular extrasystoles in CPVT are initially late-coupled (around 400 ms) and monomorphic, with a morphology suggesting an outflow tract origin in two-thirds of the cases [43]. With the continuation of the exercise, arrhythmias progressively worsen into ventricular bigeminy, couplets, and runs of bidirectional or polymorphic non-sustained VT (Fig. 13.2). Further continuation of exercise brings about the appearance of sustained VT, which may degenerate into ventricular fibrillation. Interruption of exercise leads to the regression of arrhythmias in the inverse order of appearance [1] (Fig. 13.2). It is important to consider that arrhythmias may occur also in the anticipation of exercise and that patients may spontaneously avoid or reduce physical activity due to fear of arrhythmias.

Prolonged electrocardiographic monitoring using 24-Holter ECG and/or implantable loop recorders (ILR) may complement the exercise stress test in cases when performing a diagnostically adequate exercise stress test is not feasible or in peculiar cases where emotional stress represents the most powerful trigger for arrhythmias.

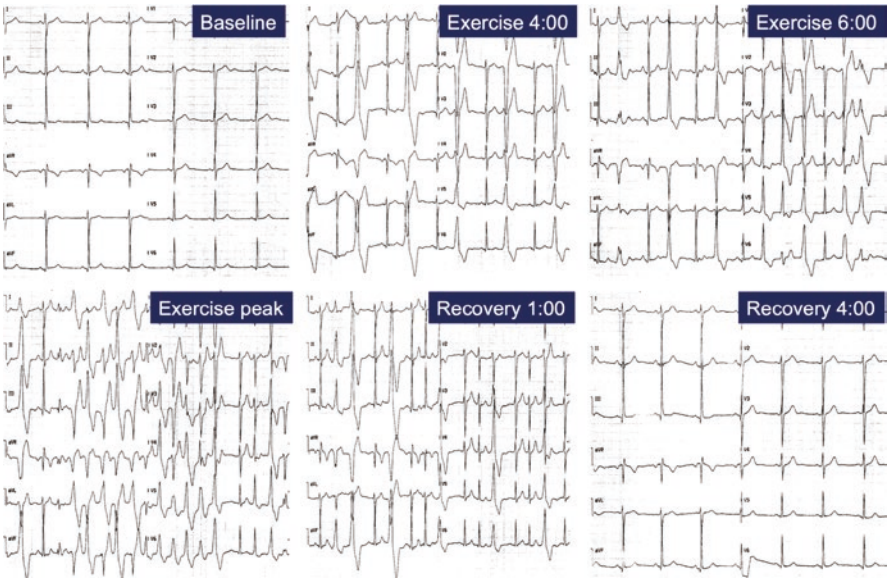

Fig. 13.2 Exercise stress test elicited arrhythmias in CPVT. As originally described by Coumel [1], the arrhythmias in CPVT start as isolated premature ventricular complexes (exercise 4:00), organizing into bigeminy and couplets (exercise 06:00), followed by the appearance of runs of non-sustained bidirectional ventricular tachycardia (exercise peak). Exercise continuation after the documentation of initial runs of non-sustained ventricular tachycardia leads to the advent of sustained ventricular tachycardia and ventricular fibrillation and is most strongly advised against it. The interruption of exercise leads to the gradual resolution of arrhythmias in the inverse order of appearance (recovery 01:00) and finally return to sinus rhythm (recovery 4:00)

An invasive electrophysiological study does not play a role in the diagnosis of CPVT, as arrhythmias are usually not inducible at programmed electrical stimulation [2].

Cardiac imaging, such as transthoracic echocardiography and/or cardiac magnetic resonance imaging, should be performed to exclude the presence of structural heart disease.

Finally, genetic testing plays an important role in the diagnosis of CPVT and should be offered to all patients with a clinical suspicion of CPVT, based on the patient's symptoms, family history, and ECG phenotype at exercise stress test, 24-h Holter ECG, or ILR. According to the current guidelines, the identification of a pathogenic *RYR2* or *CASQ2* mutation, even in the absence of the clinical phenotype, is sufficient to make the diagnosis of CPVT [2]. Variant interpretation should be done by experts in specialized centers, especially in the case of *RYR2* mutations, as it is a large [44], highly polymorphic gene with an estimated 3% of the population harboring rare but benign missense variants [45].

Following the identification of a CPVT-causative mutation index case, mutation-specific cascade genetic testing is recommended for family members [2].

13.9 Differential Diagnosis

Differential diagnosis should include other cardiac inherited arrhythmogenic disorders that can cause fatal arrhythmias, like long QT syndrome (LQTS), Andersen-Tawil syndrome, and arrhythmogenic cardiomyopathy (ACM).

Andersen-Tawil syndrome (ATS), which is caused by loss-of-function mutations of the *KCNJ2* gene, shares with the CPVT the presence of the peculiar bidirectional pattern of ventricular arrhythmias [46]. However, extra-cardiac features like periodic paralysis and skeletal dysmorphisms complete the spectrum of the clinical manifestations in ATS and can help in differentiating the two conditions [47]. Bidirectional ventricular arrhythmias in ATS, unlike CPVT, may manifest in resting conditions and not be exclusively correlated with exercise or emotion: in fact, arrhythmias may be suppressed at the peak of exercise [48, 49].

A syncopal spell occurring during adrenergic stimulation in a young patient may prompt the need for a differential diagnosis between CPVT and LQTS. Since some LQTS patients may present only a mildly prolonged QTc interval and given the catecholamine-mediated nature of arrhythmias in CPVT, an extensive clinical workup is required: 12-lead ECG, 24-h ECG Holter monitoring, and an exercise stress test. Prolongation of the QTc interval greater than 480 ms at resting 12-lead ECG or Holter monitoring clinches the diagnosis of LQTS, according to the current guidelines [2]. Exercise stress test is often decisive for the diagnosis: QTc interval prolongation during the exercise or recovery phase is suggestive for LQTS, while the induction of ventricular arrhythmias during exercise with regression in the recovery phase favors the diagnosis of CPVT. Lastly, genetic analysis can be useful to elucidate the diagnosis with the identification of causative variants in specific genes associated with LQTS or CPVT.

Finally, ventricular arrhythmias can be elicited at the exercise stress test in ACM, but at variance with CPVT, patients are usually adults and present abnormalities of the baseline ECG, along with cardiac structural abnormalities and the arrhythmias, which are usually monomorphic with a left bundle branch block pattern.

13.10 Principles of Management

The contemporary management of CPVT is based on several complementary approaches, including lifestyle modification, pharmacological treatments, left cardiac sympathetic denervation, and the use of an implantable cardioverter defibrillator (ICD).

The centerpiece of these complementary approaches is represented by the beta-blocker therapy, which is indicated in all patients with a clinical diagnosis of CPVT. We advise against the “one-size-fits-all” approach: since none of the aforementioned therapies is completely protective and all may have associated side effects, synergistic combinations have often to be adopted to fit the needs and the characteristics of each patient.

13.11 Lifestyle

As it is clear that the catecholamine release constitutes the principal trigger for VA in CPVT, current guidelines [2] recommend abstinence from competitive sports, strenuous exercise, and stressful environments for all patients with a clinical and/or genetic diagnosis of CPVT (class I recommendation, level of evidence C).

A recent observational study on a small cohort of 21 patients [50] and the latest AHA/ACC 2015 Recommendations for Competitive Athletes [51] suggested to relax the contraindication to exercise for well-treated, genotype-positive phenotype-negative patients with appropriate precautionary measures, including the acquisition of a personal automatic external defibrillator and the establishment of an emergency action plan with the appropriate school or team officials. However, it is well-known that the first manifestation of disease may be SCD, even in subjects with a previously negative exercise stress test [52]. We strongly believe that extreme caution should be exercised when making a decision, especially given that errors in judgment may lead to the sudden death of young athletes.

Importantly, all patients should be educated about the importance of strict medication adherence, since most ventricular arrhythmias are secondary to lack of compliance [7].

13.12 Pharmacological Treatment

13.12.1 Beta-Blockers

Beta-blockers, titrated to the highest maximal tolerated dose, represent the first-line therapy in all patients with a clinical diagnosis of CPVT (class I recommendation, level of evidence C) [2]. Asymptomatic family members (i.e., carriers of a pathogenic mutation who do not exhibit a clinical phenotype) should be treated with beta-blockers as well [2], as life-threatening arrhythmias may occur in the absence of treatment [52].

Some evidence exists that nonselective beta-blockers (e.g., nadolol and propranolol) are superior to selective β1-beta-blockers [53]. Although long-term outcome data on mortality are lacking, we suggest using nadolol at the dosage of 1–2 mg/kg daily in all patients with CPVT.

Although beta-blocker therapy is undoubtedly capable of changing the natural history of the disease, it reduces the risk of fatal arrhythmias but does not completely eliminate it. A large meta-analysis on the efficacy of beta-blockers including 11 series of CPVT patients demonstrated that arrhythmic event rates on beta-blocker therapy remain significant, with an estimated 8-year near-fatal and fatal event rates of 15.3% and 6.4%, respectively [54]. One of the main reasons for the failure of beta-blocker therapy is patient's noncompliance, with more than a third of events during beta-blocker therapy occurring in patients who did not take the drug on the day of the event [7].

13.12.2 Flecainide

At the current time, flecainide (2–3 mg/kg/day) in addition to beta-blockers is recommended in patients who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers (class IIa recommendation, level of evidence C) or in patient carriers of an ICD to reduce appropriate ICD shocks (class IIa recommendation, level of evidence C) [2]. Antiarrhythmic efficacy of flecainide seems to be due to the suppression of triggered beats by Na^+ channel blockade [55]. Although small retrospective [56] and randomized clinical studies [57] demonstrated the efficacy of flecainide in reducing the burden of ventricular arrhythmias, further studies proving the effect of flecainide on the long-term outcome of CPVT patients are strongly needed.

13.13 Left Cardiac Sympathetic Denervation

Left cardiac sympathetic denervation (LCSD) may be considered in patients with recurrent syncope or recurrent VT despite optimal medical therapy (class IIb recommendation according to the current guidelines, level of evidence C) [2]. This surgical procedure, usually performed using video-assisted thoracoscopic surgery (VATS), consists of the resection of the lower half of the left stellate ganglion (T1) together with the thoracic ganglia T2–T4. Importantly, it appears that LCSD does not confer complete arrhythmic protection: in a cohort of 63 symptomatic patients who underwent LCSD with a median follow-up of 37 months, 24% had at least one arrhythmic recurrence during this relatively short follow-up [58]. Some evidence suggests that LCSD may confer poorer arrhythmic protection in *CASQ2*-related CPVT [59]. Owing to the complexity of this procedure and the potential complications (e.g., Horner's syndrome or pneumothorax), this surgery should be best performed in highly specialized surgical centers.

13.14 Implantable Cardioverter Defibrillator

Current guidelines state that an implantable cardioverter defibrillator (ICD) is indicated in survivors of cardiac arrest or in patients who experienced recurrent syncope or polymorphic/bidirectional VT despite optimal therapy (class I recommendation, level of evidence C). Owing to the nature of the disease and the young age of the patients, the use of ICD needs to be weighed against the risk of inappropriate shocks and complications [60]. The ICD efficacy seems to be closely related to the underlying arrhythmia type, as episodes of ventricular fibrillation are typically successfully interrupted, whereas polymorphic or bidirectional VT tend not to be terminated by appropriate shocks [61]. It is therefore imperative to program the device carefully, with long delays before shock delivery and high cutoff rates for heart rate recognition.

13.15 Future Therapies

A number of novel pharmacological approaches for CPVT are currently under investigation. Dantrolene, which is already indicated for the treatment of malignant hyperthermia (caused by mutations in the skeletal muscle ryanodine receptor [*RYR1* gene]), has been proposed as a potential treatment for *RYR2*-related CPVT. Although the rationale for its use is solid (i.e., the stabilization of the defective interaction between the N-terminal domain and the central domain of RyR2), clinical testing has yielded mixed results [62].

On the other hand, given the role that genetics plays in the disease, the most *avant-garde* perspective for CPVT concerns the possibility of applying gene-therapy strategies. The pioneering step has been made with the demonstration that the delivery of a wild-type *CASQ2* allele using a recombinant adeno-associated viral vector was able to revert the CPVT phenotype in a mouse model of recessive CPVT [63]. This approach, called "gene transfer," was subsequently cleared for human trials by the US Food and Drug Administration (FDA). Other gene-therapy strategies, such as specific allele-silencing [64], CRISPR/Cas9-mediated gene editing [65], and cellular signaling pathway modulation (e.g. CaMKII inhibition [66, 67]) are currently in preclinical phases.

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Sport Activity in Subjects with Implantable Defibrillator

14

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14.1 Background

Physical activity is recommended worldwide according to its benefits in terms of overall cardiovascular risk reduction [1, 2]. That's true not only for healthy subjects to prevent cardiovascular diseases [3, 4] but also for cardiac patients [5]. In the last years, physical activity has been considered therapy and was tailored for each patient according to his medical history, in order to balance benefits and potential risks for adverse events.

Among cardiac patients, there is an increasing number of subjects with an implantable cardioverter defibrillator (ICD) [6], and many of them may require permission to practice sport. Potential adverse events [7–9] for this group of patients related to physical activity may be due to physical trauma (that can cause lead

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dislocation or fracture), myopotentials (with the consequence of inappropriate device shocks), inappropriate shocks due to sinus tachycardia and the risk of dizziness or pre-syncope (due to the latency between the onset of arrhythmia and ICD intervention), hypothetical undersensing of ventricular arrhythmias during strenuous physical activity.

Many of those accidents may be prevented by accurate device selection and programming. However, although uncommon, such events may be dangerous and often induce physicians to keep away their device patients from physical activity.

Therefore, it is of pivotal importance to understand indications and limitations in sport activity of ICD patients to guarantee their safety.

14.2 Epidemiology

In the last years, the number of ICD patients who practice sport is rising. Regarding young patients, a larger number of improved and anticipated diagnoses of life-threatening conditions, with consequent ICD implantation, was observed, thanks to more accurate imaging and genetic testing [10]. Even if competitive activity is often not recommended, many ICD recipients are engaged in noncompetitive sport activities. Furthermore, recent data seem to confirm that participants in recreational sports experience less frequent appropriate and inappropriate shocks during physical activity than participants in competitive sports [11].

Moreover, as populations continue to extend life expectancy, a central concern is the promotion of a high health-related quality of life into old age [12]. Physical activity is a protective factor for many diseases such as cardiovascular disease, stroke, diabetes, and some types of cancer and is associated with improved mental health, delay in the onset of dementia, and improved quality of life and well-being [13]. The number of elderly people who regularly perform physical activities is progressively increasing, and therefore, the relation between sport activity and ICD becomes crucial. The pacemaker and ICD Registry of the Italian Association of Arrhythmology and Cardiac Pacing (AIAC) reported in 2017 a number of 19,023 ICD implantations (13,898 first implants and 5125 replacements): the average age of treated patients was 71 years [14].

On the other hand, some ICD patients cannot practice sport activity because of non-eligibility: since inherited cardiomyopathies are a leading cause of sudden cardiovascular death during sports performance, the disqualification of affected people from most competitive athletic disciplines is recommended by international guidelines [15].

14.3 Cultural Aspects and Published Experiences

Recently, few retrospective studies and a large prospective registry provided some evidence for the relative safety of high-risk athletes with ICD participating in competitive sports. Nevertheless, the lack of substantial data on the natural

history of the underlying cardiac diseases and the unknown efficacy of implanted ICDs in terminating life-threatening arrhythmias during intense exercise have resulted in the restrictive nature of the guidelines regarding the eligibility for sports of ICD patients [16]. The safe participation of all athletes with an ICD in competitive sports continues to be debated despite the widespread idea that the presence of ICD makes the patient invincible and capable to take his own risk. In Italy, the national law does not allow competitive sport participation without a medical certification: sport eligibility has to be periodically renewed, and athletes have to undergo medical checks. The Italian Guidelines for Sports Eligibility in Athletes with Heart Disease (called COCIS) impose some restrictions on sport activity for ICD patients [17, 18], and this is mainly due to the prominent role of Italian Sports Federations that promotes and preserves the health of their members.

The multinational prospective ICD Sports Safety Registry has been of paramount importance in the assessment of the risks associated with sport participation in athletes with ICDs [19], as it allowed for the first time to understand which were the possible adverse events during sport practice. The authors underline that for many years, patients with ICD have been limited from participation in more vigorous sports than golf or bowling because of the allegedly higher risk of incurring ventricular arrhythmias or consequent momentary loss of physical or mental control, potential ICD failure to intervene, risk of damage to the device or leads, and other concerns. No significant difference was found between the percentage of athletes receiving an ICD shock during practice/competition and those during other physical activities (10% versus 8%, $P = 0.34$), while 6% received shocks at rest. Results from a 4-year follow-up of the same registry [20] showed that more participants received shocks during competition/practice of physical activity than at rest (20% versus 10%; $P < 0.0001$), and the appropriate shock rate was significantly greater during competition or other physical activity than at rest (11% versus 6%; $P = 0.005$), even if the proportion of patients receiving a shock during competition/practice was similar to the proportion receiving a shock during other physical activity (12% versus 10%; $P = 0.56$).

A sub-analysis of the Implantable Cardioverter Defibrillator Sports Registry [21] showed that high-rate cutoff and long detection duration programming of ICDs in athletes may reduce total and inappropriate ICD shocks, without affecting survival or the incidence of transient loss-of-consciousness. More recently, Heidbuchel and coll. [11] published data relating to arrhythmic events and lead performance in intensive recreational athletes with ICD enrolled in the European arm of the multinational ICD sport safety registry and compared their outcome with those of the competitive athletes in the registry. They found that competitive athletes received more total shocks (20.2% vs 6.3%; $P = 0.003$), with a higher number of inappropriate shocks, and both appropriate and inappropriate shocks during physical activity were more common in competitive athletes. Anyway, this study is limited by the fact that the shock report was given by the athletes and a possible underestimation of the real number of shocks has to be taken into account.

14.4 Actual Recommendations (Tables 14.1, 14.2, and 14.3)

Actual recommendations on sport activity in patients with a CIED derive from consensus documents and experts' opinions (class of recommendations B and C) and based largely on reasoned notions, given the limited exhaustiveness of existing data. In many countries, there is no specific legislation for sport practice, and when available, there are substantial differences between them.

A Scientific Statement From the American Heart Association and American College of Cardiology published in 2015 [22] was mainly focused on competitive sport, while ESC Guidelines include leisure activity [23], but both share the concept that the desire of the athlete to continue athletic competition should not represent the primary indication for the use of an ICD.

In detail, American guidelines [22] provide some generic statements suggesting that ICD indications for competitive athletes should not differ from those applicable to the general population and that recommendations should be based on existing evidence for benefit and risk and should include discussions of the potential impact on sport-specific participation and performance. Participation in sports classified as IA (bowling, cricket, curling, golf, rifler, and yoga) is considered reasonable if they are free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months (Class IIa; Level of Evidence C). In class IIb and level of evidence

Table 14.1 Indications for physical activity in ICD competitive athletes according to AHA/ACC Scientific Statement 2015 [22]

	Indications	Class	Level
Recommendations for sports classified as IA	Participation in sports classified as IA for athletes with an ICD is reasonable if they are free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months	IIa	C
Recommendations for sports than class IA	Participation in sports with higher peak static and dynamic components than class IA may be considered if the athlete is free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months. The decision regarding athletic participation should be made with consideration of, and counseling of, the athlete regarding the higher likelihood of appropriate and inappropriate shocks and the potential for device-related trauma in high-impact sports	IIb	C
Recommendations for exercise in individuals with ICD	ICD indications for competitive athletes should not differ from those applicable to the general population with appropriate diagnoses and clinical profiles	I	C
	Recommendations should be based on existing evidence for benefit and risk and should include discussions of the potential impact on sport-specific participation and performance	I	C
	The desire of the athlete to continue athletic competition should not represent the primary indication for use of an ICD	III	C

ICD implantable cardioverter defibrillator

Table 14.2 Indications for physical activity in ICD competitive athletes according to Italian Guidelines—COCIS [24]

	Indications
Idoneity for competitive sport	Nontraumatic sport
	Asymptomatic subjects
	Low- or mild-intensity sports
	At least 3 months from the latest ICD antiarrhythmic intervention (appropriate or non-appropriate)
	Normal cardiac function or mild to moderate cardiac function impairment
	Underlying heart disease compatible with sport
Non-idoneity for competitive sport	Underlying heart disease not compatible with sport
	Traumatic sport
	High-intensity sports
	Sport requiring repetitive movement of the arm corresponding to the implant site (for transvenous ICDs)

Table 14.3 Indications for physical activity in ICD patients according to ESC Guidelines 2020 [23]

	Indications	Class	Level
Brugada syndrome	Following implantation of an ICD, resumption of leisure or competitive sports should be considered after shared decision making in individuals who have not experienced recurrent arrhythmias over 3 months after ICD implantation	IIa	C
Long QT syndrome	Participation in competitive sports (with or without ICD) is not recommended in individuals with LQTS and prior cardiac arrest or arrhythmic syncope	III	C
Recommendations for exercise in individuals with PM and ICD	It is recommended that individuals with implanted devices with/without resynchronization and underlying disease follow the recommendations pertaining to the underlying disease	I	B
	Shared decision-making should be considered during decisions relating to continuation of intensive or competitive sport participation in individuals with an ICD, taking into account the effect of sports on the underlying substrate, the fact that intensive sports will trigger more appropriate and inappropriate shocks, the psychological impact of shocks on the athlete/patient, and the potential risk for third parties	IIa	C
	An ICD is not recommended as a substitute for disease-related recommendations when these mandate sports restrictions	III	C

PM pacemaker, *ICD* implantable cardioverter defibrillator

C, it is affirmed that participation in sports with higher peak static and dynamic components than class IA may be considered if the athlete is free of episodes of ventricular flutter or ventricular fibrillation requiring device therapy for 3 months. The decision regarding athletic participation should be made with consideration of and counseling of the athlete regarding the higher likelihood of appropriate and inappropriate shocks and the potential for device-related trauma in high-impact sports.

In Italy, indications regarding competitive sports and leisure activity have been issued by COCIS ("Comitato Organizzativo Cardiologico per l'Idoneità allo Sport," which means: Italian Cardiological Guidelines for Sports Eligibility) in 2017 [24]. An international update version of COCIS is being reviewed for publication in J Cardiovasc Medicine. In the Italian document, it is stated that sport eligibility cannot be considered for traumatic activities and in patients with an underlying heart disease noncompatible with sport. It is suggested to consider for eligibility only asymptomatic subjects, at least 3 months after the latest device intervention (appropriate or inappropriate). Only subjects with normal or moderately compromised cardiac function can be included. Eligibility can be considered only for low- and moderate-intensity sports.

Many of these Italian recommendations have been translated into the recent ESC Guidelines, underlying that "shared decision-making should be considered during decisions relating to continuation of intensive or competitive sport participation in individuals with an ICD, taking into account the effect of sports on the underlying substrate, the fact that intensive sports will trigger more appropriate and inappropriate shocks, the psychological impact of shocks on the athlete/patient, and the potential risk for third parties" [23].

14.5 Subcutaneous ICD

The subcutaneous ICD can be considered a useful tool for athletic patients at risk of sudden death [25, 26]: it solves potential lead problems due to mechanical stresses, and with dedicated algorithm, it has the potential to reduce the incidence of inappropriate shocks. Subcutaneous ICD features seem very appealing in young and physically active subjects, with long life expectancy that increases the probability of a lead fracture. However, some questions remain unsolved, like the ones concerning the underlying disease. Physical activity has a negative impact on the progression of some cardiac conditions (for example, hypertrophic and arrhythmogenic cardiomyopathy) that are not modified by the kind of implanted device. Moreover, this solution is not suitable for patients with ICD and indications for pacing, cardiac resynchronization therapy, or anti-tachycardia pacing.

14.6 Discussion and Perspectives

The previous guidelines described a lot of restrictions for patients with ICD. In the most recent versions, revised and updated, the competitive sports might be considered for this group of patients, even if of low-moderate cardiovascular demand. The

registries with longer-term data have shown a higher percentage of shocks during physical activity than at rest [19]. This highlights the importance of tailoring the exercise to avoid the risk of shock, appropriate or not. On the other hand, too restrictive indications can limit the patients and stop their physical activity, preventing those subjects from the general health benefits of exercise.

Exercise has a positive effect in improving physical function and the overall quality of life, mitigating stress, and reducing hospitalizations and outpatient visits [27]. The question is to balance the potential risk in sport participation for ICD patients with the demonstrated adverse effects of physical inactivity [9].

Moreover, even when physical activity is allowed, the rationale of the indications described in guidelines is in contrast with the general idea of "sport" that in the collective imaginary usually means great physical involvement. The clinician's intention to preserve patients' health and life could be not appreciated by patients. Moreover, the difference between competitive and leisure time sport activity is not so rigorous, and it could be confusing for patients and clinicians and the broad spectrum of cardiomyopathy that make it difficult to extrapolate general considerations on this category of subjects.

To overcome this, a clear discussion of the case with the patient, or his parents in case of minors, can be useful. Evidences and common sense encourage us to share the often complex decision process with the patient/athlete, giving him information about potential risks of an adverse event that could occur during physical activity.

Another important aspect is the possible evolution of underlying pathology, such as in the case of arrhythmogenic or hypertrophic cardiomyopathy: physical exercise could represent in these cases an arrhythmic trigger and could improve cardiomyopathy progression [28, 29] and creating an unstable substrate that increases susceptibility to sudden cardiac death [30]. Careful device programming is necessary to guarantee an adequate physical performance [9, 21] and to minimize the risk of inappropriate shocks of ICD, which creates poor acceptance of the ICD, shock anxiety, and poor quality of life [31]. If well-chosen and programmed, the device could represent a very useful tool for obtaining data regarding the arrhythmic burden of the underlying disease during physical activity. Further preimplantation assessment is necessary for young athletic patients, regarding the number of leads to implant, to balance the risks related to lead extraction and/or placement of additional leads and the ventricular arrhythmia detection thanks to the atrial electrogram. A decision-making process with the direct involvement of the electrophysiologist for a proper device choice and setup is recommended.

Sport activity in ICD patients is a hot topic with several concerns: every kind of sports (competitive or not) may represent not only a risk but also a benefit for patients with ICD, if performed safely. The challenge in the next years will be the possibility of individualizing the recommendations, supporting the patients in choosing the most suitable activity for their clinical condition. Device set-up should be personalized and tailored, also with the help of remote home monitoring.

Furthermore, the improvement of device materials and technology will support patients and clinicians in the decisions. Until then, in our daily practice, caution, common sense, and open discussion with single patients are tricks up our sleeve.

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